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(71) Applicant (*for all designated States except US*): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): CHAKRAVARTY, Prasun, K. [IN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). NARGUND, Ravi [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MARQUIS, Robert, W. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). PATCHETT, Arthur, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). YANG, Lihu [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

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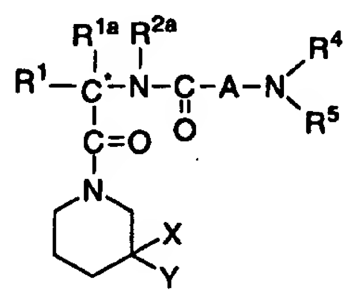
(54) Title: 3-SUBSTITUTED PIPERIDINES PROMOTE RELEASE OF GROWTH HORMONE

(57) Abstract

The present invention is directed to certain novel compounds identified as 3-substituted piperidines of general structural formula (I): wherein R^1, R^{1a}, R^{2a}, R^4, R^5, A, X, and Y are as defined herein. These compounds promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to treat physiological or medical conditions characterized by a deficiency in growth hormone secretion, such as short stature in growth hormone deficient children, and to treat medical conditions which are improved by the anabolic effects of growth hormone. Growth hormone releasing compositions containing these compounds as the active ingredient thereof are also disclosed.



(I)

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TITLE OF THE INVENTION

3-SUBSTITUTED PIPERIDINES PROMOTE RELEASE OF GROWTH HORMONE

BACKGROUND OF THE INVENTION

Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic processes of the body: (1) Increased rate of protein synthesis in all cells of the body; (2) Decreased rate of carbohydrate utilization in cells of the body; (3) Increased mobilization of free fatty acids and use of fatty acids for energy. A deficiency in growth hormone secretion can result in various medical disorders, such as dwarfism.

Various ways are known to release growth hormone. For example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering GRF or a peptidal compound which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone. Recombinant growth hormone has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which

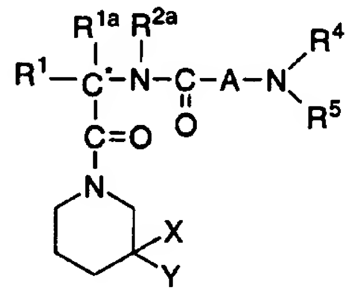
must be given by injection or by a nasal spray. Other compounds have been developed which stimulate the release of endogenous growth hormone such as analogous peptidyl compounds related to GRF or the peptides of U.S. Patent 4,411,890. These peptides, while considerably smaller than growth hormones are still susceptible to various proteases. As with most peptides, their potential for oral bioavailability is low. Non peptidal growth hormone secretagogues with a benzolactam structure are disclosed in e.g., U.S. Patent Nos 5,206,235, 5,283,241, 5,284,841, 5,310,737 and 5,317,017. Other growth hormone secretagogues are disclosed in PCT Patent Publications WO 94/13696 and WO 94/19367. The instant compounds are low molecular weight peptide analogs for promoting the release of growth hormone which have good stability in a variety of physiological environments and which may be administered parenterally, nasally or by the oral route.

SUMMARY OF THE INVENTION

The instant invention is directed to certain 3-substituted piperidine compounds which have the ability to stimulate the release of natural or endogenous growth hormone. The compounds thus have the ability to be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food or wool production where the stimulation of growth hormone will result in a larger, more productive animal. Thus, it is an object of the instant invention to describe the 3-substituted piperidine compounds. It is a further object of this invention to describe procedures for the preparation of such compounds. A still further object is to describe the use of such compounds to increase the secretion of growth hormone in humans and animals. A still further object of this invention is to describe compositions containing the 3-substituted piperidine compounds for the use of treating humans and animals so as to increase the level of growth hormone secretions. Further objects will become apparent from a reading of the following description.

DESCRIPTION OF THE INVENTION

The novel 3-substituted piperidines of the instant invention are described by structural Formula I:



Formula I

wherein:

R^1 is selected from the group consisting of:
C_1-C_{10} alkyl, aryl, aryl(C_1-C_6 alkyl), (C_3-C_7 cycloalkyl)(C_1-C_6 alkyl)-, (C_1-C_5 alkyl)-K-(C_1-C_5 alkyl)-, aryl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-, and (C_3-C_7 cycloalkyl)(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-, where K is -O-, -S(O)$_m$-, -N(R^2)C(O)-, -C(O)N(R^2)-, -OC(O)-, -C(O)O-, -CR^2=CR^2-, or -C≡C-, where aryl is selected from: phenyl, naphthyl, indolyl, azaindole, pyridyl, benzothienyl, benzofuranyl, thiazolyl, and benzimidazolyl, and R^2 and alkyl may be further substituted by 1 to 9 halogen, S(O)$_m$$R^{2a}$, 1 to 3 of O$R^{2a}$ or C(O)OR^{2a}, and aryl may be further substituted by 1 to 3 of C_1-C_6 alkyl, 1 to 3 of halogen, 1 to 2 of -OR^2, methylenedioxy, -S(O)$_m$$R^2$, 1 to 2 of -$CF_3$, -O$CF_3$, nitro, -N($R^2$)C(O)($R^2$), -C(O)O$R^2$, -C(O)N($R^2$)($R^2$), -1H-tetrazol-5-yl, -$SO_2$N($R^2$)($R^2$), -N($R^2$)$SO_2$ phenyl, or -N(R^2)$SO_2$$R^2$;

R^{1a} is selected from hydrogen and C_1-C_6 alkyl;

R^2 is selected from: hydrogen, C_1-C_6 alkyl, and C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring, optionally including oxygen, sulfur or NR^{3a}, where R^{3a} is hydrogen, or C_1-C_6 alkyl, optionally substituted by hydroxyl;

R^{2a} is selected from hydrogen and C_1-C_6 alkyl;

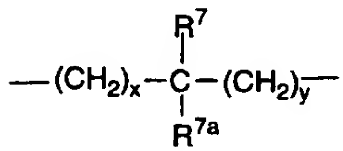
R^4 and R^5 are independently hydrogen, C_1-C_6 alkyl, or substituted C_1-C_6 alkyl where the substituents are selected from: 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenyloxy, 2-furyl, C_1-C_6 alkoxycarbonyl, $S(O)_m(C_1$-C_6 alkyl), or R^4 and R^5 may be taken together to form $-(CH_2)_d$-$L_a(CH_2)_e$- where L_a is $-C(R^2)_2$-, -O-, $-S(O)_m$- or $-N(R^2)$-, d and e are independently 1 to 3 and R^2 is as defined above;

X is selected from the group consisting of:
$-(CH_2)_qN(R^8)C(O)R^2$, $-(CH_2)_qN(R^8)C(O)R^8$,
$-(CH_2)_qN(R^8)C(O)OR^2$, $-(CH_2)_qN(R^8)C(O)OR^8$,
$-(CH_2)_qN(R^8)C(O)OR^2$, $-(CH_2)_qN(R^2)C(O)OR^8$,
$-(CH_2)qN(R^8)C(O)OR^8$, $-(CH_2)_qN(R^2)SO_2R^9$, $-(CH_2)_qN(R^8)SO_2R^8$,
$-(CH_2)qN(R^8)SO_2R^2$, $-(CH_2)_qN(R^2)SO_2N(R^2)(R^2)$,
$-(CH_2)_qN(R^2)SO_2N(R^2)(R^8)$, $-(CH_2)_qN(R^8)C(O)N(R^2)(R^2)$,
$-(CH_2)_qN(R^8)C(O)N(R^2)(R^8)$, $-(CH_2)qSO_2N(R^2)(R^2)$,
$-(CH_2)qSO_2N(R^2)(R^8)$, $-(CH_2)_qN(R^2)(R^8)$, and $-(CH_2)_qR^{10}$,
where the R^2 and $(CH_2)_q$ groups may be optionally substituted by 1 to 2 C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, $CONH_2$, $S(O)_mCH_3$, carboxylate C_1-C_4 alkyl esters, or 1H-tetrazol-5-yl;

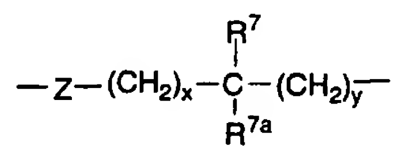
Y is selected from the group consisting of:
hydrogen, C_1-C_{10} alkyl, $-(CH_2)_t$aryl, $-(CH_2)_q(C_3$-C_7 cycloalkyl), $-(CH_2)_q$-K-(C_1-C_6 alkyl), $-(CH_2)_q$-K-$(CH_2)_t$aryl, $-(CH_2)_q$-K-$(CH_2)_t(C_3$-C_7 cycloalkyl containing -O-, $-NR^2$-, or -S-), and $-(CH_2)_q$-K-$(CH_2)_t(C_3$-C_7 cycloalkyl), where K is as defined above, and where the alkyl, R^2, $(CH_2)_q$ and $(CH_2)_t$ groups may be optionally substituted by C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, $-CONH_2$ or carboxylate C_1-C_4 alkyl esters, and where aryl is phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl,

isoxazolyl, thiopheneyl, quinolinyl, pyrazinyl, or isothiazolyl which is optionally substituted by 1 to 3 halogen, 1 to 3 -OR^2, -$C(O)OR^2$, -$C(O)N(R^2)(R^2)$, nitro, cyano, benzyl, 1 to 3 C_1-C_4 alkyl, -$S(O)_mR^2$, or 1H-tetrazol-5-yl;

A is:



or



where x and y are independently 0, 1, 2 or 3;

Z is -$N(R^{6a})$- or -O-, where R^{6a} is hydrogen or C_1-C_6 alkyl;

R^7 and R^{7a} are independently hydrogen, C_1-C_6 alkyl, trifluoromethyl, phenyl, or substituted C_1-C_6 alkyl where the substituents are imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, -OR^2, -$S(O)_mR^2$, -$C(O)OR^2$, C_3-C_7 cycloalkyl, -$N(R^2)(R^2)$, -$C(O)N(R^2)(R^2)$, or R^7 and R^{7a} may independently be joined to one or both of R^4 and R^5 groups to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R^7 or R^{7a} groups, wherein the bridge contains 1 to 5 carbons atoms, or R^7 and R^{7a} can be joined to one another to form C_3-C_7 cycloalkyl;

R^8 is -$(CH_2)_p$aryl, where aryl is selected from: phenyl, naphthyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, thienyl, pyrazinyl, pyrimidinyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, indolyl, quinolinyl, and isoquinolinyl, and where the aryl is optionally substituted with 1 to 2 of halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, or -$C(O)N(R^2)(R^2)$;

R^9 is selected from the group consisting of: isoxazolyl, thiazolyl, isothiazolyl, thienyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, indolyl, quinolinyl, and isoquinolinyl, which

are optionally substituted by 1 to 2 of halogen, $-R^2$, $-OR^2$, $-N(R^2)(R^2)$, $-C(O)OR^2$, or $-C(O)N(R^2)(R^2)$;

R^{10} is selected from the group consisting of: 1,2,4-oxadiazolyl, pyrazinyl, triazolyl, and phthalimidoyl, which are optionally substituted with $-R^2$, $-OR^2$ or $-N(R^2)(R^2)$;

m is 0, 1, or 2;
p is 0, 1, 2, or 3;
q is 0, 1, 2, 3, or 4;
t is 0, 1, 2, or 3;
and pharmaceutically acceptable salts and individual diastereomers thereof.

In the above structural formula and throughout the instant specification, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration and if two carbon atoms or more they may include a double or a triple bond. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, allyl, propargyl, and the like.

The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration and if two or more carbon atoms in length, they may include a double or a triple bond. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propargyloxy, and the like.

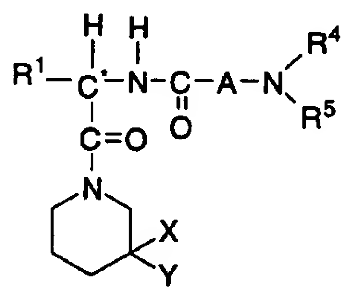
The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine.

The term "aryl" within the present invention, unless otherwise specified, is intended to include aromatic rings, such as carbocyclic and heterocyclic aromatic rings selected the group consisting

of: phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiopheneyl, quinolinyl, pyrrazinyl, or isothiazolyl, which may be optionally substituted by 1 to 3 of C_1-C_6 alkyl, 1 to 3 of halogen, 1 to 2 of -OR^2, methylenedioxy, -$S(O)_mR^2$, 1 to 2 of -CF_3, -OCF_3, nitro, -$N(R^2)C(O)(R^2)$, -$C(O)OR^2$, -$C(O)N(R^2)(R^2)$, -1H-tetrazol-5-yl, -$SO_2N(R^2)(R^2)$, -$N(R^2)SO_2$ phenyl, or -$N(R^2)SO_2R^2$, wherein R^2 is as defined herein.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other.

Preferred compounds of the instant invention include those of Formula Ia:



Formula Ia

wherein:

R^1 is selected from the group consisting of:

C_1-C_{10} alkyl, aryl (C_1-C_4 alkyl)-, C_3-C_6 cycloalkyl (C_1-C_4 alkyl)-, (C_1-C_4 alkyl)-K-(C_1-C_2 alkyl)-, aryl (C_0-C_2 alkyl)-K-(C_1-C_2 alkyl)-, and (C_3-C_7 cycloalkyl)(C_0-C_2 alkyl)-K-(C_1-C_2 alkyl)-, where K is -O-, -$S(O)_m$-, -OC(O)-, or -C(O)O-, and the alkyl groups may be further substituted by 1 to 7 halogen, -$S(O)_mR^2$, 1 to 3 -OR^2 or -$C(O)OR^2$, and aryl is phenyl, naphthyl, indolyl, pyridyl, benzimidazolyl, azaindolyl, benzothienyl or benzofuranyl which may be further substituted by 1-2 C_1-C_4 alkyl, 1 to 2 halogen, 1 to 2 -OR^2, -$S(O)_mR^2$, or -$C(O)OR^2$;

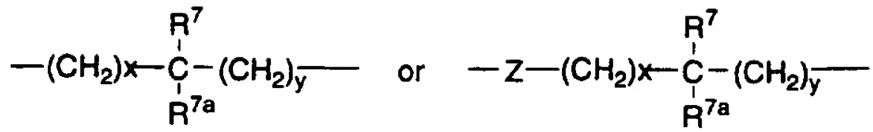
R^2 is hydrogen, C_1-C_6 alkyl, or C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom they may be optionally joined to form a C_4-C_7 cyclic ring optionally including oxygen, sulfur or NR^{3a};

R^4 and R^5 are independently hydrogen, C_1-C_6 alkyl, or substituted C_1-C_6 alkyl where the substituents are 1 to 5 halo, 1 to 3 hydroxyl, -S(O)m (C_1-C_6 alkyl) or phenyl;

X is selected from the group consisting of:
-$(CH_2)_qN(R^8)C(O)R^2$, -$(CH_2)_qN(R^8)C(O)R^8$, -$(CH_2)_qN(R^8)C(O)OR^2$, -$(CH_2)_qN(R^8)C(O)OR^8$, -$(CH_2)_qN(R^8)C(O)OR^2$, -$(CH_2)_qN(R^2)C(O)OR^8$, -$(CH_2)qN(R^8)C(O)OR^8$, -$(CH_2)_qN(R^2)SO_2R^9$, -$(CH_2)_qN(R^8)SO_2R^8$, -$(CH_2)qN(R^8)SO_2R^2$, -$(CH_2)_qN(R^2)SO_2N(R^2)(R^2)$, -$(CH_2)_qN(R^2)SO_2N(R^2)(R^8)$, -$(CH_2)_qN(R^8)C(O)N(R^2)(R^2)$, -$(CH_2)_qN(R^8)C(O)N(R^2)(R^8)$, -$(CH_2)qSO_2N(R^2)(R^2)$, -$(CH_2)qSO_2N(R^2)(R^8)$, -$(CH_2)_qN(R^2)(R^8)$, and -$(CH_2)_qR^{10}$, where the R^2, and $(CH_2)_q$ groups are optionally substituted by 1 to 2 C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, $CONH_2$, $S(O)_mCH_3$, carboxylate C_1-C_4 alkyl esters, or 1H-tetrazol-5-yl;

Y is selected from the group consisting of:
hydrogen, C_1-C_8 alkyl, $(CH_2)_t$aryl, -(CH_2)q(C_5-C_6 cycloalkyl), -(CH_2)q-K-(C_1-C_6 alkyl), -(CH_2)q-K-$(CH_2)_t$aryl, -$(CH_2)_q$-K-$(CH_2)_t$(C_3-C_7 cycloalkyl containing -O-, -NR^2-, or -S-), and -(CH_2)q-K-$(CH_2)_t$ (C_5-C_6 cycloalkyl), where K is -O- or -S(O)m- and where the alkyl groups are optionally substituted by hydroxyl, carboxyl, $CONH_2$, carboxylate C_1-C_4 alkyl esters or 1H-tetrazole-5-yl and aryl is phenyl, naphthyl, pyridyl, 1-H-tetrazolyl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, or thiopheneyl which is optionally substituted by 1 to 3 halogen, 1 to 3 -OR^2, -$C(O)OR^2$, -$C(O)N(R^2)(R^2)$, cyano, 1 to 2 C_1-C_4 alkyl, benzyl, -$S(O)_mR^2$, or 1H-tetrazol-5-yl-;

A is:



where x and y are independently 0, 1 or 2;

Z is $-NR^{6a}-$ or -O-, where R^{6a} is hydrogen or C_1-C_3 alkyl;

R^7 and R^{7a} are independently hydrogen C_1-C_6 alkyl, trifluoromethyl, phenyl, substituted C_1-C_6 alkyl where the substituents are imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, OR^2, $S(O)mR^2$, $C(O)OR^2$, C_5-C_7 cycloalkyl, $-N(R^2)(R^2)$, $-C(O)N(R^2)(R^2)$; or R^7 and R^{7a} can independently be joined to one of R^4 or R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of R^7 or R^{7a} groups to form 5 or 6 membered rings; or R^7 and R^{7a} can be joined to one another to form a C_3 cycloalkyl;

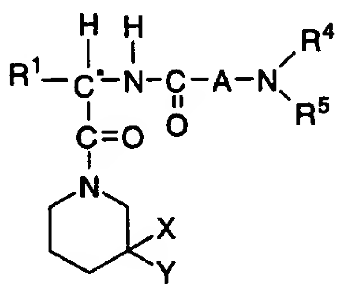
R^8 is $-(CH_2)_p$aryl, where aryl is selected from: phenyl, naphthyl, pyridyl, thiazolyl, isothiazolyl, oxaxolyl, isoxazolyl, thienyl, pyrazinyl, pyrimidinyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, indolyl, quinolinyl, and isoquinolinyl, and where aryl may be substituted by 1 to 2 of halogen, $-R^2$, $-OR^2$, $-N(R^2)(R^2)$, $-C(O)OR^2$, or $-C(O)N(R^2)(R^2)$;

R^9 is selected from the group consisting of: isoxazolyl, thiazolyl, isothiazolyl, thienyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, indolyl, quinolinyl, and isoquinolinyl, which may be substituted by 1 to 2 of halogen, $-R^2$, $-OR^2$, $-N(R^2)(R^2)$, $-C(O)OR^2$, or $-C(O)N(R^2)(R^2)$;

R^{10} is selected from the group consisting of: 1,2,4-oxadiazolyl, pyrazinyl, triazolyl, and phthalimidoyl, which are optionally substituted with $-R^2$, $-OR^2$ or $-N(R^2)(R^2)$;

m is 0, 1 or 2;
p is 0, 1 or 2;
q is 0, 1 or 2;
t is 0, 1 or 2;
and pharmaceutically acceptable salts and individual diastereomers thereof.

More preferred compounds of the instant invention include those of Formula Ib:



Formula 1b

wherein:

R^1 is selected from the group consisting of: C_1-C_{10} alkyl, aryl (C_1-C_3 alkyl)-, (C_3-C_7 cycloalkyl)(C_1-C_3 alkyl)-, and aryl (C_0-C_1 alkyl)-K-(C_1-C_2 alkyl)-, where K is O or $S(O)_m$ and the aryl is phenyl, pyridyl, naphthyl, indolyl, azaindolyl, benzothienyl, or benzimidazolyl which is optionally substituted by 1-2 C_1-C_4 alkyl, 1 to 2 halogen, 1 to 2 -OR^2, -$S(O)_mR^2$, or $C(O)OR^2$;

R^2 is hydrogen, C_1-C_6 alkyl, or C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom they may be optionally joined to form a C_5-C_7 cyclic ring optionally including oxygen, sulfur or NR^{3a};

R^4 and R^5 are independently hydrogen, C_1-C_4 alkyl, or substituted C_1-C_3 alkyl where the substituents may be 1 to 2 hydroxyl;

X is selected from the group consisting of:

$-(CH_2)_qN(R^8)C(O)R^2$, $-(CH_2)_qN(R^8)C(O)R^8$, $-(CH_2)_qN(R^8)C(O)OR^2$, $-(CH_2)_qN(R^8)C(O)OR^8$, $-(CH_2)_qN(R^8)C(O)OR^2$, $-(CH_2)_qN(R^8)C(O)OR^8$, $-(CH_2)_qN(R^2)SO_2R^9$, $-(CH_2)_qN(R^8)SO_2R^8$, $(CH_2)_qN(R^8)SO_2R^2$, $-(CH_2)_qN(R^8)C(O)N(R^2)(R^2)$, $-(CH_2)_qN(R^8)C(O)N(R^2)(R^8)$, $-(CH_2)_qSO_2N(R^2)(R^2)$, $-(CH_2)_qSO_2N(R^2)(R^8)$, $-(CH_2)_qN(R^2)(R^8)$, and $-(CH_2)_qR^{10}$, where the R^2, and $(CH_2)_q$ groups may be optionally substituted by 1 to 2 C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, $-CONH_2$, $-S(O)_mCH_3$, carboxylate C_1-C_4 alkyl esters, or 1H-tetrazol-5-yl;

Y is selected from the group consisting of: hydrogen, C_1-C_8 alkyl, $(CH_2)_t$aryl, $-(CH_2)_q$ C_5-C_7 cycloalkyl, $-(CH_2)_q$-K-(C_1-C_6 alkyl), $-(CH_2)_q$-K-$(CH_2)_t$aryl, and $-(CH_2)_q$-K-$(CH_2)_t$ (C_5-C_6 cycloalkyl), where K is $S(O)_m$ and where the alkyl groups may be optionally substituted by hydroxyl, carboxyl, $CONH_2$, carboxylate C_1-C_4 alkyl esters or 1H-tetrazole-5-yl and aryl is phenyl, naphthyl, indolyl, pyridyl, thiazolyl, thiopheneyl, pyrazolyl, oxazolyl, isoxazolyl or imidazolyl which may be optionally substituted by 1 to 2 halogen, 1 to 2 $-OR^2$, 1 to 2 $-N(R^2)(R^2)$, $-CO(OR^2)$, 1 to 2 C_1-C_4 alkyl, $-S(O)_mR^2$, or 1H-tetrazol-5-yl;

A is:

$$-(CH_2)_x-\underset{R^{7a}}{\overset{R^7}{C}}-(CH_2)_y- \quad \text{or} \quad -Z-(CH_2)_x-\underset{R^{7a}}{\overset{R^7}{C}}-(CH_2)_y-$$

where x and y are independantly 0 or 1; Z is $-N(R^{6a})-$ or -O-, where R^{6a} is hydrogen or C_1-C_3 alkyl;

R^7 and R^{7a} are independently hydrogen, C_1-C_6 alkyl, phenyl, substituted C_1-C_6 alkyl wherein the substitutent is imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, $-OR^2$, $-S(O)_mR^2$, or R^7 and R^{7a} can

independently be joined to one of R^4 or R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portions of R^7 or R^{7a} groups to form 5 or 6 membered rings; or R^7 or R^{7a} can be joined to one another to form a C_3-C_6 cycloalkyl;

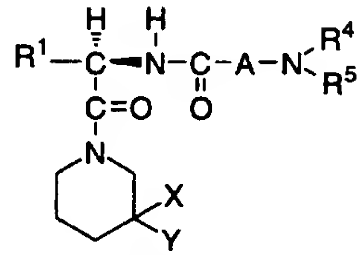
R^8 is -(CH2)paryl, where aryl is selected from: phenyl, naphthyl, pyridyl, thiazolyl, isothiazolyl, oxaxolyl, isoxazolyl, thienyl, pyrazinyl, pyrimidinyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, indolyl, quinolinyl, and isoquinolinyl, and where aryl may be substituted by 1 to 2 of halogen, $-R^2$, $-OR^2$, $-N(R^2)(R^2)$, $-C(O)OR^2$, or $-C(O)N(R^2)(R^2)$;

R^9 is selected from the group consisting of: isoxazolyl, thiazolyl, isothiazolyl, indolyl, thienyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, quinolinyl, and isoquinolinyl, which may be substituted by 1 to 2 of halogen, $-R^2$, $-OR^2$, $-N(R^2)(R^2)$, $-C(O)OR^2$, or $-C(O)N(R^2)(R^2)$;

R^{10} is selected form the group consisting of: 1,2,4-oxadiazolyl, pyrazinyl, and triazolyl which may be substituted by $-R^2$, $-OR^2$, or $-N(R^2)(R^2)$;

m is 0, 1, or 2;
p is 0, 1, or 2
q is 0, 1,or 2;
t is 0, 1, or 2;
and pharmaceutically acceptable salts and individual diastereomers thereof.

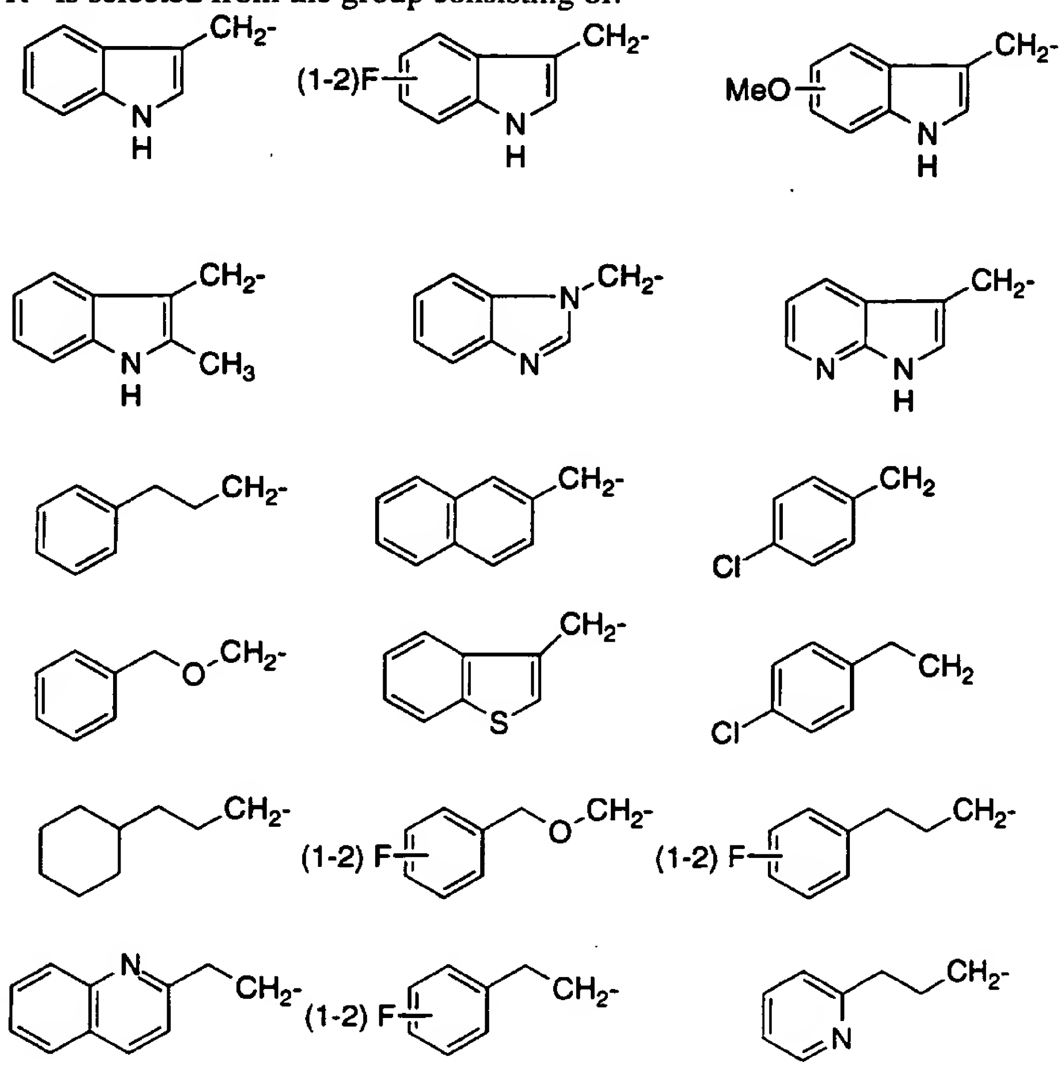
Still more preferred compounds of the instant invention include those of Formula Ic:



Formula Ic

wherein:

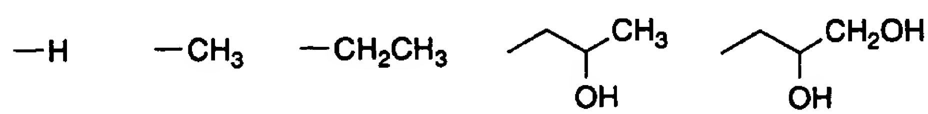
R[1] is selected from the group consisting of:



or their regioisomers where not specified;

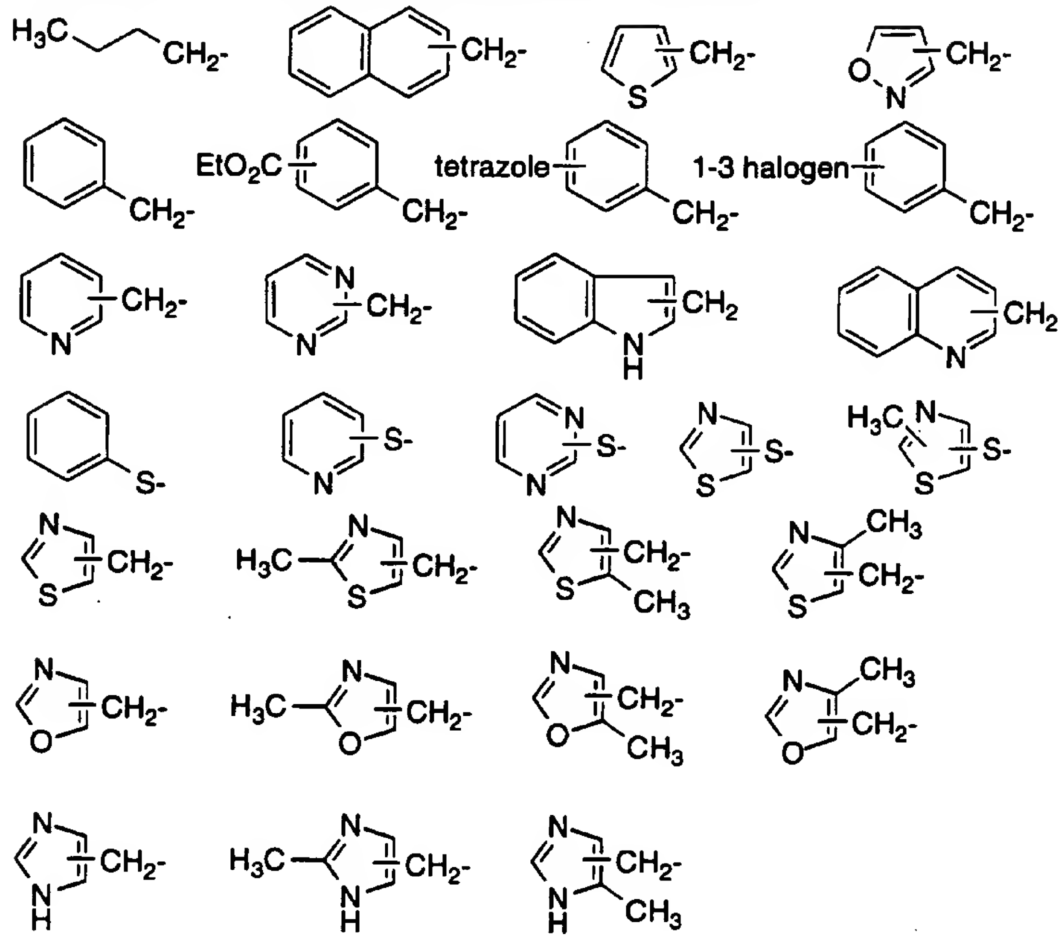
R^2 is hydrogen, C_1-C_6 alkyl, or C_3-C_7 cycloalkyl and where two C_1-C_6 alkyl groups are present on one atom they may be optionally joined to form a C_5-C_7 cyclic ring optionally including oxygen, sulfur or NR^{3a};

R^4 and R^5 are independently selected from the group consisting of:



X is selected from the group consisting of:
$-(CH_2)qN(R^8)C(O)R^2$, $-(CH_2)qN(R^8)C(O)R^8$,
$-(CH_2)qN(R^8)C(O)OR^2$, $-(CH_2)qN(R^2)C(O)OR^8$,
$-(CH_2)qN(R^8)C(O)OR^8$, $-(CH_2)qN(R^2)SO_2R^9$, $-(CH_2)qN(R^8)SO_2R^8$,
$-(CH_2)qN(R^8)SO_2R^2$, $-(CH_2)qN(R^2)SO_2N(R^2)(R^2)$,
$-(CH_2)qN(R^2)SO_2N(R^2)(R^8)$, $-(CH_2)qN(R^8)C(O)N(R^2)(R^2)$,
$-(CH_2)qN(R^8)C(O)N(R^2)(R^8)$, and $-(CH_2)_qN(R^2)(R^8)$;

Y is selected from the group consisting of: hydrogen,



or their regioisomers whereof where not specified;

A is:

$$-(CH_2)_x-\underset{R^{7a}}{\overset{R^7}{\underset{|}{\overset{|}{C}}}}-(CH_2)_y- \quad \text{or} \quad -Z-(CH_2)_x-\underset{R^{7a}}{\overset{R^7}{\underset{|}{\overset{|}{C}}}}-(CH_2)_y-$$

where x and y are independently 0 or 1;

Z is $-(NR^{6a})-$ or -O-, where R^{6a} is hydrogen or C_1-C_6 alkyl;

R^7 and R^{7a} are independently C_1-C_6 alkyl and substituted C_1-C_6 alkyl wherein the substituent is phenyl, naphthyl or indolyl or R^7 and R^{7a} can independently be joined to one of the R^4 or R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portions of R^7 or R^{7a} to form 5 or 6 membered rings;

R^8 is $(CH_2)_p$aryl where aryl is selected from: phenyl, naphthyl, pyridyl, pyrazinyl, pyrimidinyl, thiazolyl, indolyl, quinolinyl and isoquinolinyl and where the aryl may be substituted by 1 to 2 halogen, $-R^2$, $-OR^2$, $N(R^2)(R^2)$, $-C(O)OR^2$ or $-C(O)N(R^2)(R^2)$;

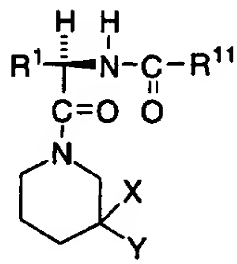
R^9 is selected from the group consisting of: isoxazolyl, thiazolyl, indolyl, quinolinyl and isoquinolinyl, which may be substituted by 1 to 2 halogen, $-R^2$, $-OR^2$, $-N(R^2)(R^2)$, $-C(O)OR^2$ or $-C(O)N(R^2)(R^2)$;

R^{10} is 1,2,4-oxadiazolyl which may be substituted by $-R^2$, $-OR^2$, or $-N(R^2)(R^2)$;

m is 0, 1 or 2;
p is 0 or 1;
q is 0 or 1;
t is 0 or 1;

and pharmaceutically acceptable salts and individual diasteromers thereof.

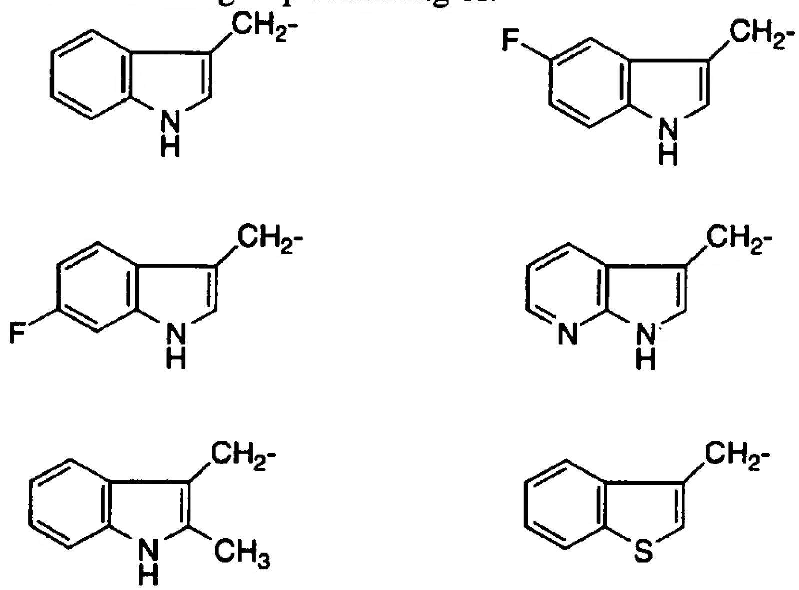
The most preferred compounds of the instant invention include those of Formula Id:



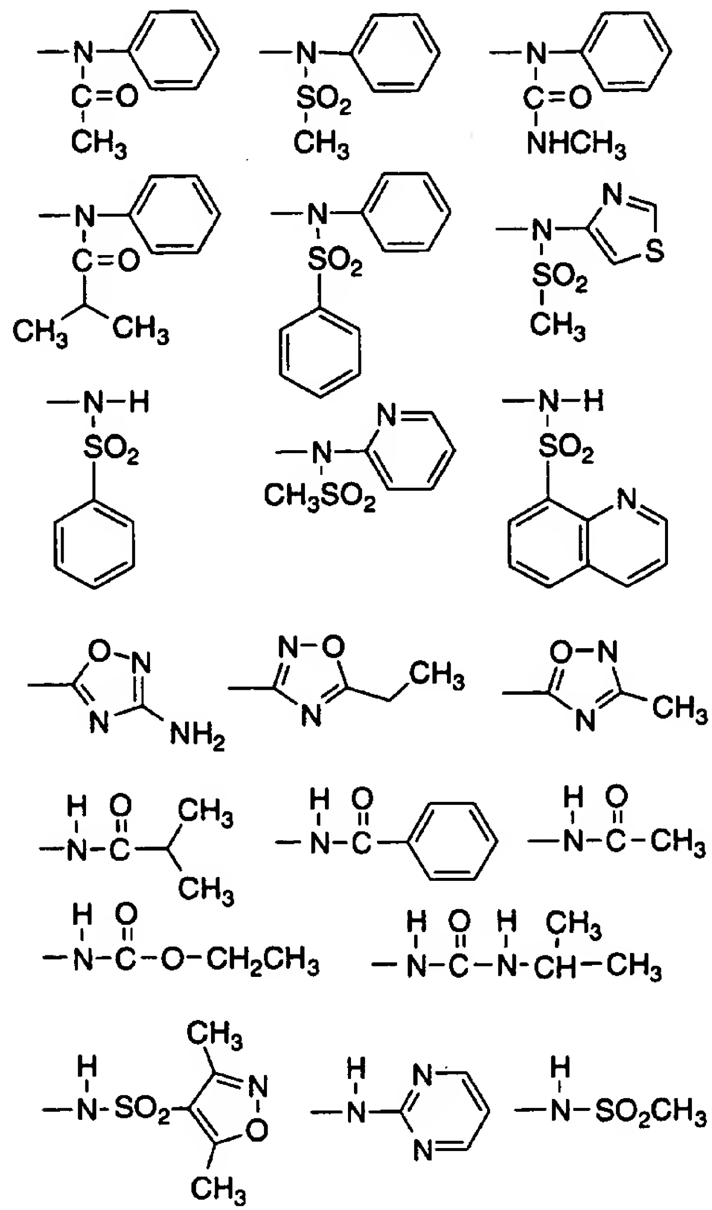
Formula Id

wherein:

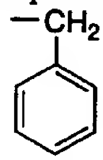
R^1 is selected from the group consisting of:

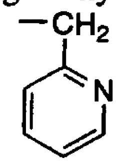


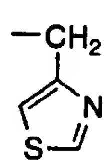
X is selected from the group consisting of:

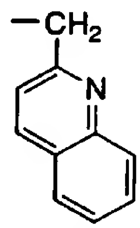


Y is selected from the group consisting of: hydrogen,



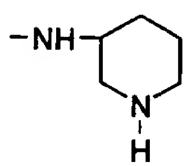


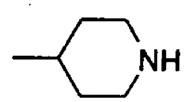


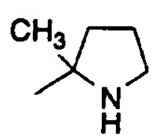


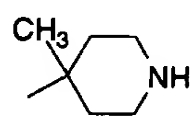
R^{11} is selected from the group consisting of:

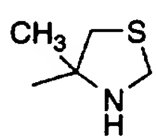
$-CH_2C(CH_3)_2NH_2$ $-C(CH_3)_2NH_2$

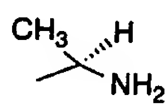












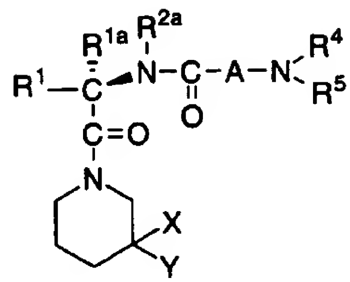
and pharmaceutically acceptable salts and individual diasteromers thereof.

Throughout the instant application, the following abbreviations are used with the following meanings:

Bu	butyl
Bn	benzyl
BOC, Boc	t-butyloxycarbonyl
BOP	Benzotriazol-1-yloxy tris/dimethylamino)-phosphonium hexafluorophosphate
calc.	calculated
CBZ, Cbz	Benzyloxycarbonyl
DCC	Dicyclohexylcarbodiimide
DMF	N,N-dimethylformamide
DMAP	4-Dimethylaminopyridine
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide hydrochloride
EI-MS	Electron ion-mass spectroscopy
Et	ethyl
eq.	equivalent(s)
FAB-MS	Fast atom bombardment-mass spectroscopy
HOBT, HOBt	Hydroxybenztriazole
HPLC	High pressure liquid chromatography
KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminum hydride
LHMDS	Lithium bis(trimethylsilyl)amide
Me	methyl
MF	Molecular formula
MHz	Megahertz
MPLC	Medium pressure liquid chromatography
NMM	N-Methylmorpholine
NMR	Nuclear Magnetic Resonance
Ph	phenyl
Pr	propyl
prep.	prepared
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

TLC	Thin layer chromatography
TMS	Tetramethylsilane

The compounds of the instant invention all have at least two asymmetric centers when both X and Y are groups other than hydrogen and are different from each other. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixture and as pure or partially purified compounds are included within the ambit of this invention. In the case of the asymmetric carbon atom represented by an asterisk in Formula I, it has been found that compounds are more active as growth hormone secretagogues and, therefore preferred, in which the nitrogen substituent is above and the hydrogen atom is below the plane of the structure as represented in Formula II. An equivalent representation places R^1 and the N-substitutent in the plane of the structure with the C=O group above. This configuration corresponds to that present in a D-amino acid. In most cases, this is also designated an R-configuration, although this will vary according to the value of R^1 used in making R- or S- stereochemical assignments. In the case of the asymmetric center which bears the X and Y groups, in most cases, both R- and S- configurations are consistent with useful levels of growth hormone secretagogue activity. In addition configurations of many of the most preferred compounds of this invention are indicated. When the carbon atom in Formula I bearing an asterisk is of a defined and usually a D- configuration, two diastereomers result according to the absolute configuration at the carbon atom bearing the X and Y groups. These diastereomers are arbitrarily referred to as diastereomer 1 (d_1) and diastereomer 2 (d_2) in this invention and, if desired, their independent syntheses or chromatographic separations may be achieved as described herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.



Formula II

The instant compounds are generally isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic, methane sulfonic and the like. In addition, certain compounds containing an acidic function such as a carboxy can be isolated in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

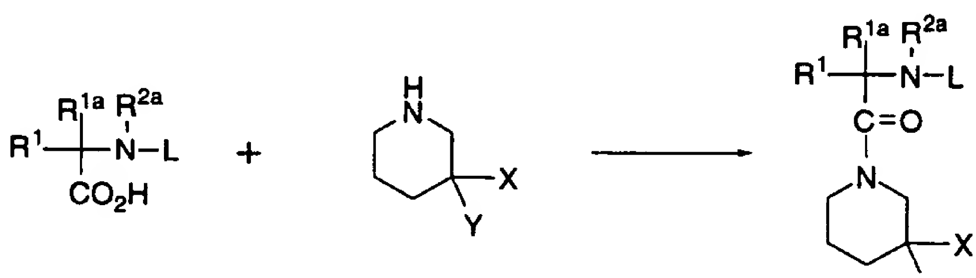
The preparation of compounds of Formula I of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses detailing the preparation of the compounds of Formula I in a sequential manner are presented in the following reaction schemes.

The phrase "standard peptide coupling reaction conditions" is used repeatedly here, and it means coupling a carboxylic acid with an amine using an acid activating agent such as EDC, DCC, and BOP in a inert solvent such as dichloromethane in the presence of a catalyst such as HOBT. The uses of protective groups for amine and carboxylic acid to facilitate the desired reaction and minimize undesired reactions are well documented. Conditions required to remove protecting groups which may be present and can be found in Greene, T, and Wuts, P. G. M., *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, NY 1991. CBZ and BOC were used extensively in the synthesis, and their removal conditions are known to those skilled in the art. For example, removal of CBZ groups can be achieved by a number of methods known in the art; for example, catalytic hydrogenation with

hydrogen in the presence of a nobel metal or its oxide such as palladium on activated carbon in a protic solvent such as ethanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, removal of CBZ groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid, or by treatment with a mixture of TFA and dimethylsulfide. Removal of BOC protecting groups is carried out in a solvent such as methylene chloride or methanol or ethyl acetate, with a strong acid, such as trifluoroacetic acid or hydrochloric acid or hydrogen chloride gas.

The protected amino acid derivatives 1 are, in many cases, commercially available, where the protecting group L is, for example, BOC or CBZ groups. Other protected amino acid derivatives 1 can be prepared by literature methods (Williams, R. M. *Synthesis of Optically Active α-Amino Acids*, Pergamon Press: Oxford, 1989). Many of the piperidines, pyrrolidines, and hexahydro-1H-azepines of Formula 2 are either commercially available or known in the literature and others can be prepared following literature methods described for analogous compounds. Some of these methods are illustrated in the subsequent schemes. The skills required in carrying out the reaction and purification of the resulting reaction products are known to those in the art. Purification procedures includes crystallization, normal phase or reverse phase chromatography.

SCHEME 1

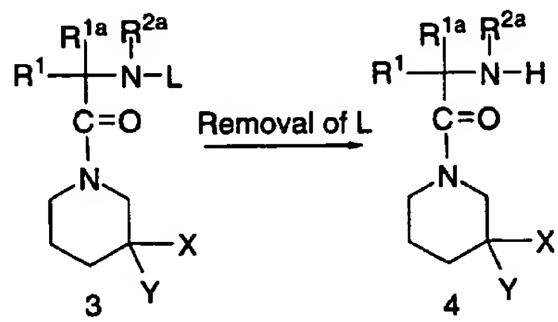


1 2 3

Intermediates of Formula 3 may be synthesized as described in Scheme 1. Coupling of amine of Formula 2, whose preparations are described later if they are not commercially available, to protected amino

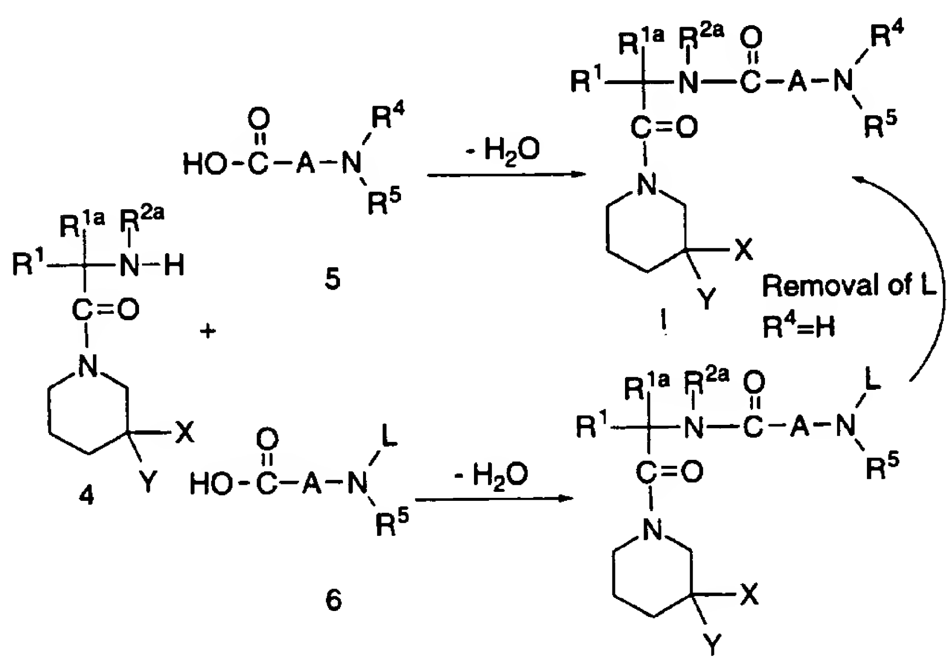
acids of Formula 1, wherein L is a suitable protecting group, is conveniently carried out under standard peptide coupling conditions.

SCHEME 2



Conversion of 3 to intermediate 4 can be carried out as illustrated in Scheme 2 by removal of the protecting group L (CBZ, BOC, etc.)

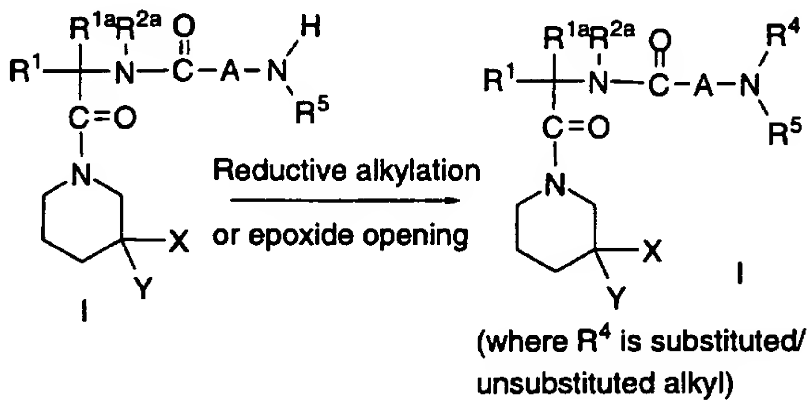
SCHEME 3



Intermediates of Formula 5, wherein A is -(CH2)x-C(R^7)(R^{7a})-(CH2)y- may be coupled to intermediates of Formula 4 to

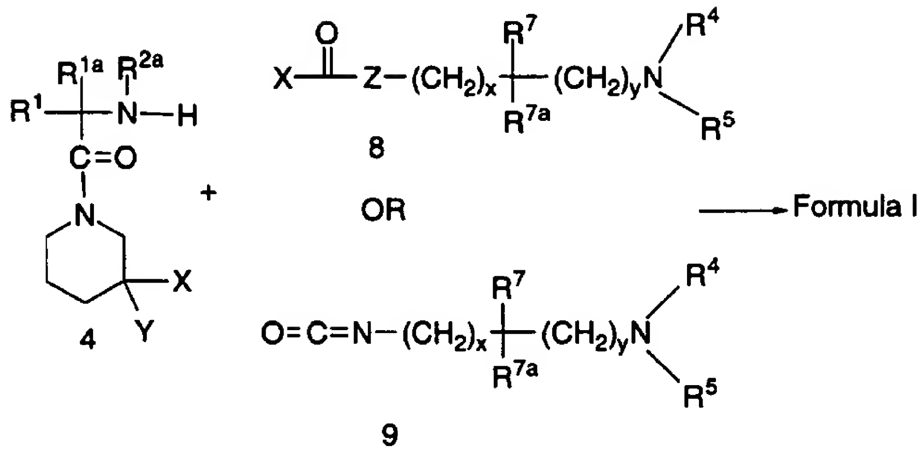
afford compounds of Formula I under standard peptide coupling reaction conditions. The amino acids 5, as amino acid 1, are either commercially available or can be synthesized by routine methods. Also if R^4 or R^5 is a hydrogen then the protected amino acids 6 are employed in the coupling reaction, wherein L is a protecting group as defined above. The removal of L in 7 to afford I, where R^4 = H, can be carried out as noted above.

SCHEME 4



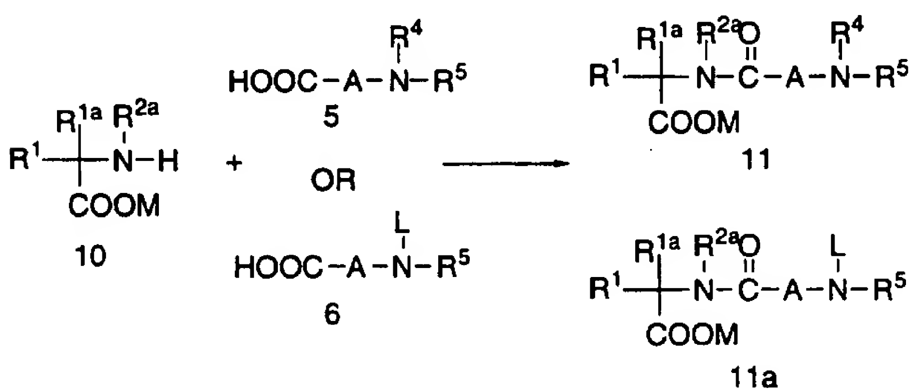
Compounds of Formula I wherein R^4 and/or R^5 is a hydrogen may be further elaborated to new Compounds I (with side chains $R^4 = R^2$ or CH_2-CH(OH)-CH_2X, wherein X = H or OH) which are substituted on the amino group as depicted in Scheme 4. Reductive alkylation of I with an aldehyde is carried out under conditions known in the art; for example, by catalytic hydrogenation with hydrogen in the presence of platinum, palladium, or nickel catalysts or with chemical reducing agents such as sodium cyanoborohydride in a protic solvent such as methanol or ethanol in the present of catalytic amount of acid. Alternatively, a similar transformation can be accomplished via an epoxide opening reaction.

SCHEME 5



Compounds of Formula I, wherein A is Z-$(CH_2)_x$-$C(R^7)(R^{7a})$-$(CH_2)_y$ and Z is N-R^{6a} or O may be prepared as shown in Scheme 5 by reacting 4 with reagents 8, wherein X is a good leaving group such as Cl, Br, I, or imidazole. Alternatively, 4 may be reacted with an isocyanate of Formula 9 in an inert solvent such as 1,2-dichloroethane to provide compounds of Formula I where Z is NH.

SCHEME 6

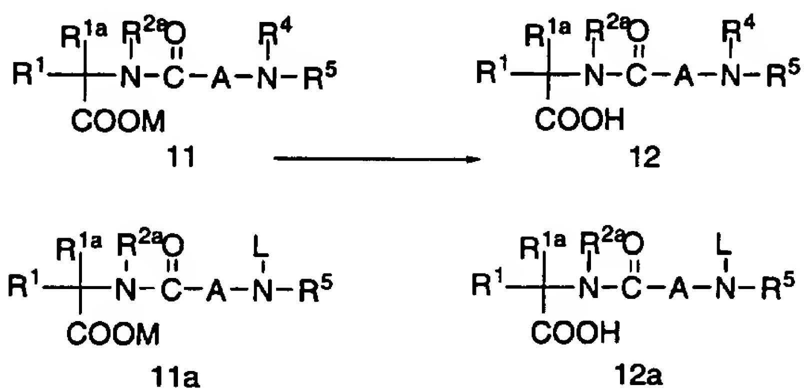


The compounds of general Formula I of the present invention may also be prepared in a convergent manner as described in reaction Schemes 6, 7 and 8.

The carboxylic acid protected amino acid derivatives 10 are, in many cases, commercially available where M = methyl, ethyl, or benzyl esters. Other ester protected amino acids can be prepared by classical methods familiar to those skilled in the art. Some of these methods include the reaction of the amino acid with an alcohol in the presence of an acid such as hydrochloric acid or p-toluenesulfonic acid and azeotropic removal of water. Other reactions includes the reaction of a protected amino acid with a diazoalkane, or with an alcohol and an acid activating agent such as EDC, DCC in the presence of a catalyst such as DMAP and removal of the protecting group L.

Intermediates of Formula 11 or 11a, may be prepared as shown in Scheme 6 by coupling of amino acid ester 10 to amino acids of Formula 5 or 6. When a urea or carbamate linkage is present in 11 or 11a, it can be introduced as illustrated in Scheme 5.

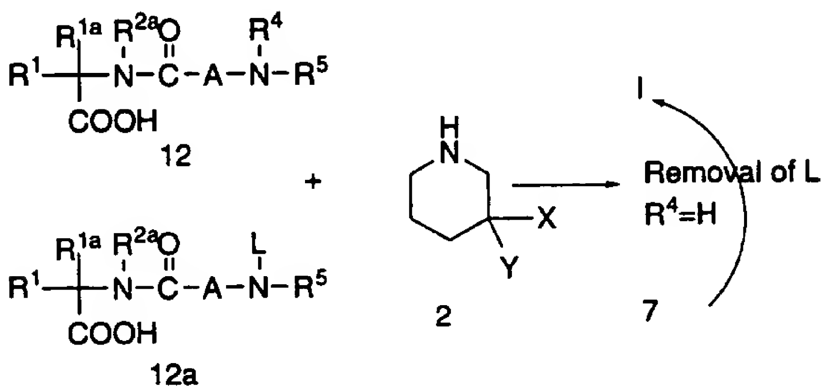
SCHEME 7



Conversion of the ester 11 or 11a to intermediate acids 12 or 12a may be achieved by a number of methods known in the art as described in Scheme 7; for example, methyl and ethyl esters can be hydrolyzed with lithium hydroxide in a protic solvent like aqueous methanol. In addition, removal of benzyl group can be accomplished by a number of reductive methods including hydrogenation in the presence of palladium catalyst in a protic solvent such as methanol. An allyl ester can be cleaved with tetrakis-triphenylphosphine palladium catalyst in the

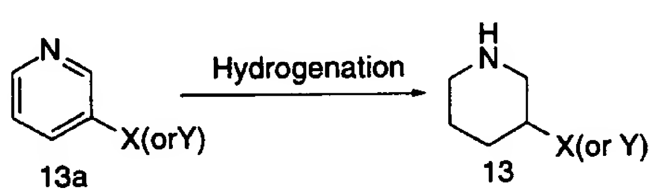
presence of 2-ethylhexanoic acid in a variety of solvents including ethyl acetate and dichloromethane (see J. Org. Chem., 42, 587 (1982)).

SCHEME 8



Acid 12 or 12a may then be elaborated to I or to I bearing protecting group L (Compound I) as described in Scheme 8. Coupling of piperidines of Formula 2 to acids of Formula 12 or 12a, is conveniently carried out under the standard peptide coupling reaction conditions. Transformation of 7 to I is achieved by removal of the protecting group L. When R^4 and/or R^5 is H, substituted alkyl groups may be optionally added to the nitrogen atom as described in Scheme 4.

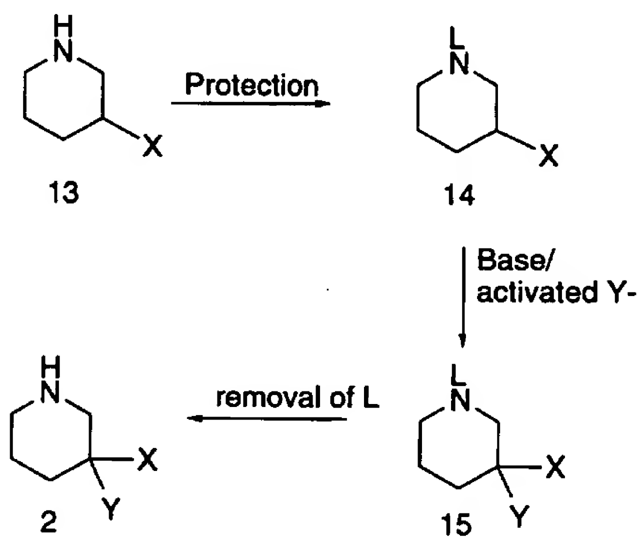
SCHEME 9



3-Monosubstituted piperidines of formula 13 can be prepared by the reduction of pyridine derivatives or their salts by hydrog-nation in a suitable organic solvent such as water, acetic acid, alcohol, e.g. ethanol, or their mixture, in the presence of a noble metal catalyst such as platinum or an oxide thereof on a support such as activated carbon, and conveniently at room temperature and atmospheric

pressure or under elevated temperature and pressure. 3-Monosubstituted piperidines can also be prepared by modification of the X or Y moiety of the existing 3-monosubstituted piperidines.

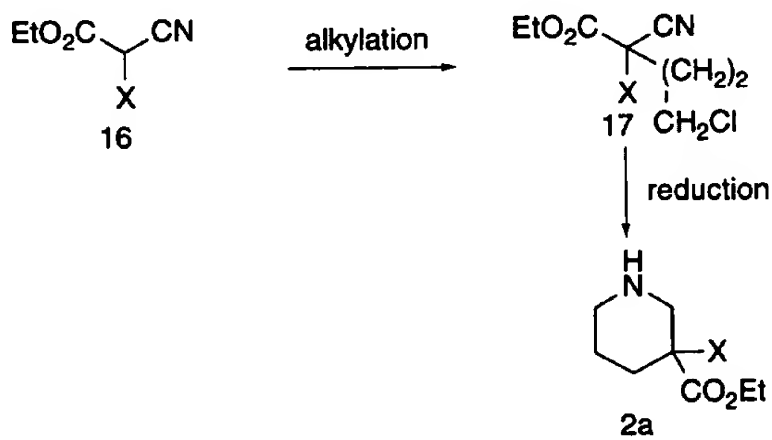
SCHEME 10



Illustrated in Scheme 10 is a general way to prepare di-substituted piperidines. Compounds of Formula 13 wherein X is an electron withdrawing group such as -CN, $-CO_2R^2$, where R^2 is alkyl, aryl, and (C_1-C_4alkyl)aryl are known compounds or may be prepared by methods analogous to those used for the preparation of such known compounds. The secondary amine of compounds of Formula 13 may be first protected by a protecting group L such as BOC and CBZ using the conventional techniques. Introduction of the Y substitution can be achieved by first reacting compounds of Formula 14 with a strong base such as lithium bis(trimethylsilyl)amide, lithium diisopropylamide following by addition of alkylating or acylating reagents such as alkyl halides, aryl alkyl halides, acyl halides, and haloformates in a inert solvent such as THF at temperatures from -100°C to room temperature. Thio derivatives where the sulfur is attached directly to an alkyl or an aryl group can be prepared similarly by reacting with a disulfide. The halides used in these reactions are either commercially available or

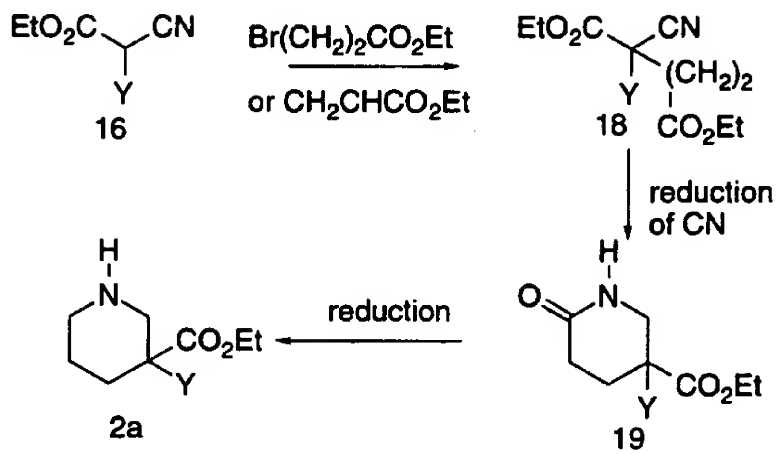
known compounds in the literature or may be prepared by methods analogous to those used for the preparation of known compounds. The protecting group L in compounds of formula 15 may be removed with conventional chemistry to give compounds of Formula 2.

SCHEME 11



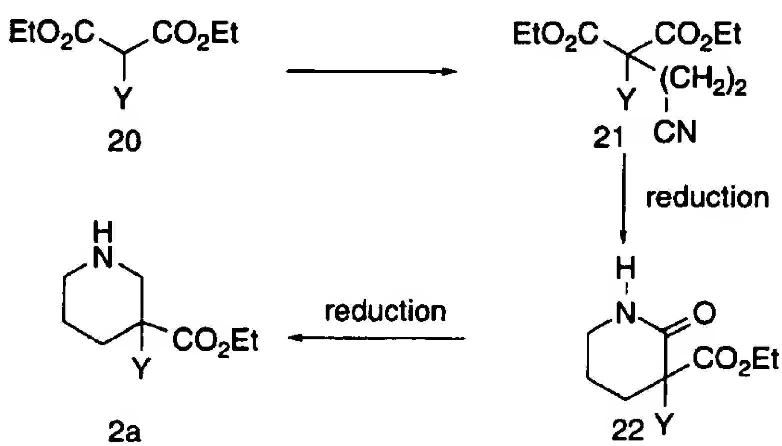
Alternative ways of preparing compounds of Formula 2 include construction of the ring itself (Jacoby, R. L. et al, J. Med. Chem., 17, 453-455, (1974)). Alkylation of the cyanoacetates of general formula 16, which are commercially available or may be prepared from literature procedures, with alkyl dihalides such as 1-bromo-2-chloroethane or 1-bromo-3-chloropropane yields the chloride 17. Reduction of the nitriles 17 by borane or by hydrogenation using Raney Ni as a catalyst gives the corresponding primary amines, which upon refluxing in ethanol give compounds of Formula 2a.

SCHEME 12



Alternatively, the cyanoacetates of general formula 16 may be alkylated with an ethoxycarbonylalkyl bromide or reacted with ethyl acrylate to give compounds of Formula 18. Reduction of the nitriles 18 by borane or by hydrogenation using Raney Ni as a catalyst gives the corresponding primary amines, which upon refluxing in ethanol gives lactam 19. Reduction of the lactam 19 by borane gives compounds of Formula 2a.

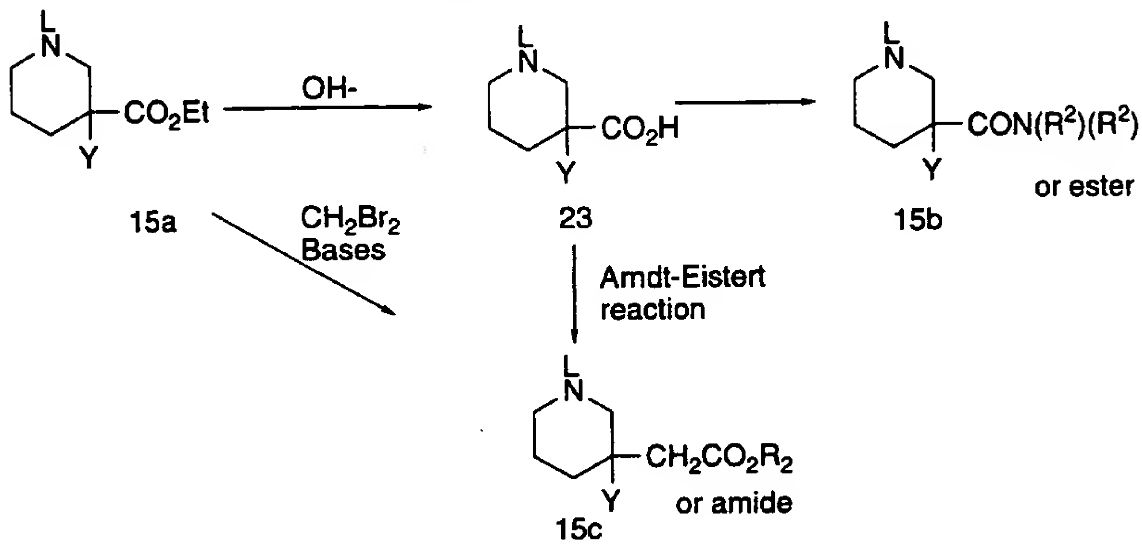
SCHEME 13



Alternatively, a malonate of general formula 20 may be alkylated with cyanoalkyl bromide or can be reacted with acrylonitrile to form compounds of formula 21. Reduction of the nitriles 21 by borane or

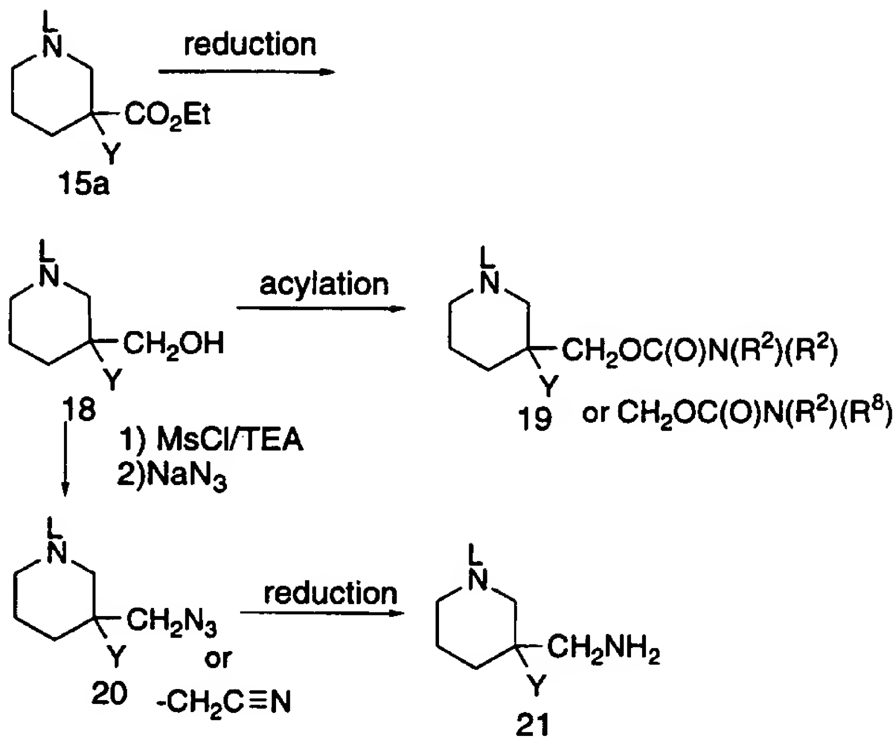
by hydrogenation using Raney Ni as a catalyst gives the corresponding primary amines, which upon refluxing in ethanol gives lactam 22. Reduction of the lactam 22 by borane gives compounds of formula 2a.

SCHEME 14



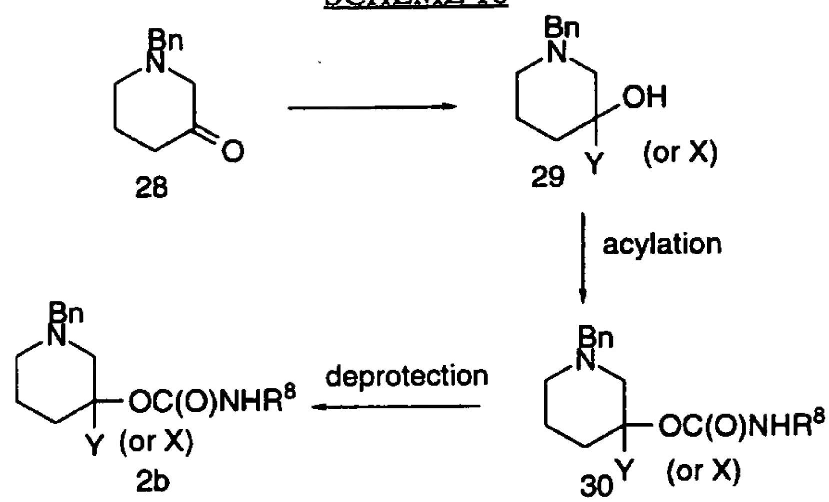
The X, Y functionalities in compounds of general structure 15 may be further elaborated to groups not accessible by direct alkylation. For example in Compound 15 when X = CO2Et the ester (provided that this is the only ester group in the molecule) can be saponified to the carboxylic acid, which can be further derivatized to amides or other esters. The carboxylic acid can be converted into its next higher homologue, or to a derivative of the homologous acid, such as amide or ester by an Arndt-Eistert reaction. Alternatively, the ester can be directly homologated by the protocol using ynolate anions described by C. J. Kowalski and R. E. Reddy in J. Org. Chem., 57, 7194-7208 (1992). The resulting acid and/or ester may be converted to the next higher homologue, and so on and so forth. The protecting group L may be removed through conventional chemistry.

SCHEME 15



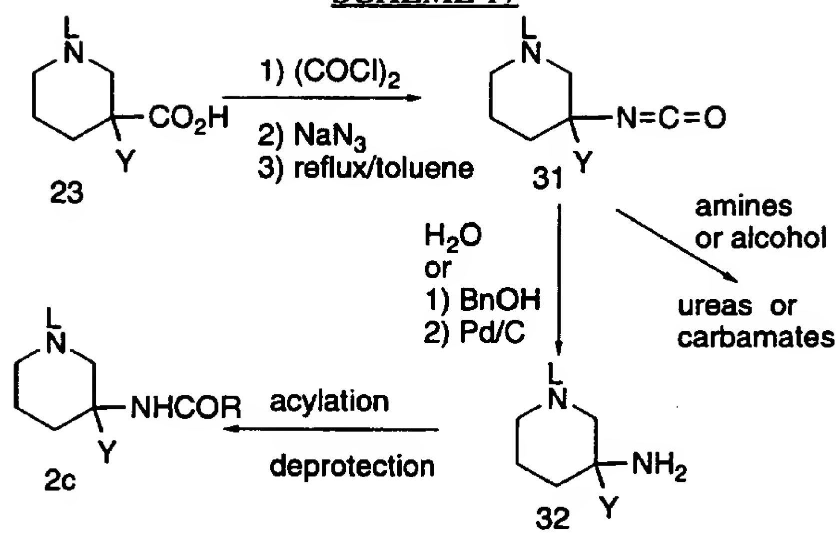
The ester in 15a may be reduced to an alcohol 18 in a suitable solvent such as THF or ether with a reducing agent such as DIBAL-H and conveniently carried out at temperatures from -100°C to 0°C. The alcohol may be converted to Compound 19 in a suitable solvent such as dichloromethane using the corresponding isocyanate or with a reagent such as T-C(O)N(R^2)(R^8) where T is leaving group like p-nitrophenol. The hydroxy group in 18 may also be converted to a good leaving group such as mesylate and displaced by a nucleophile such as cyanide or an azide. Reduction of the azide in compounds of Formula 20 to an amine 21 can be achieved by hydrogenation in the presence of a noble metal such as palladium or its oxide or Raney nickel in a protic solvent such as ethanol. The nitrile can be reduced to afford the homologous amine. The amine of Formula 21 may be further elaborated to amides, ureas sulfonamides as defined by X through conventional chemistry. The protecting group L may be removed through conventional chemistry.

SCHEME 16



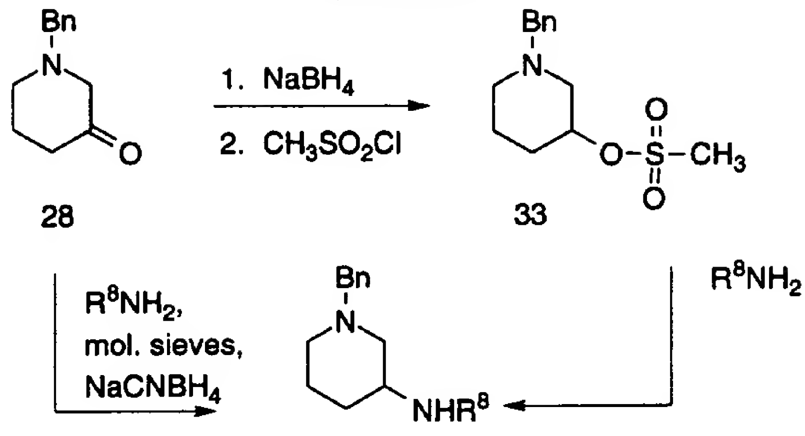
In cases where oxygen is directly attached to the ring, a convenient method involves the addition reaction by an activated form of an alkyl, aryl, alkylaryl group, such as lithium reagent, Grignard reagents, and the like with a ketone of general formula 28, which is commercially available. Further derivatization of the resulting hydroxy group by reaction with isocyanates or with T-C(O)N(R^8)(R^2) where T is leaving group like p-nitrophenol or N-hydroxysuccinimide and the like gives compounds as defined by Y or X through conventional chemistry. Removal of the benzyl protective group may be carried out under the usual conditions to give compounds of general formula 2b. Shown in Scheme 16 is a general example of acylations.

SCHEME 17



In cases where a nitrogen-substituted group is directly attached to the ring, a convenient method is to use the Curtius rearrangement on the acid 23 to afford the isocyanate 31. Addition of amines or alcohols give ureas or carbamates respectively which can be deprotected to remove L to give special cases of compounds of formula 2. Conversion of the isocyanate to amine by hydrolysis gives compound 32. Further derivatization of the resulting amine group by acylation, sulfonylation, alkylation, and the like to give compounds as defined by Y or X can be done through conventional chemistry. Removal of the protective group L may be carried out under the usual conditions to give compounds of general formula 2c. Shown in Scheme 17 is a general example of acylations.

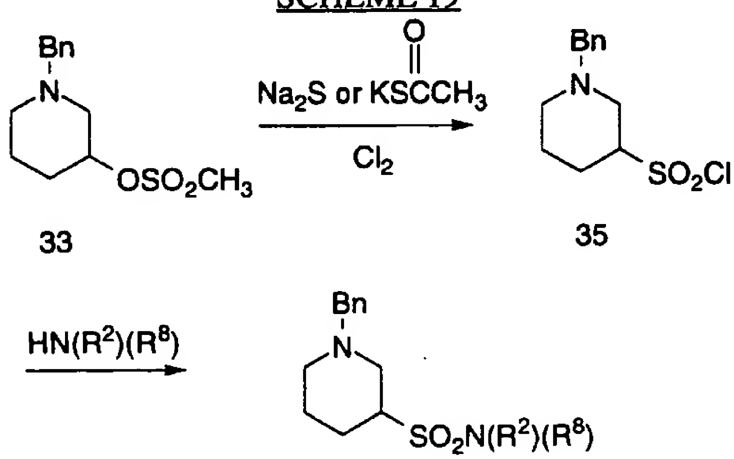
SCHEME 18



28 33 34

Compounds of formula 34 may also be prepared from N-protected 3-piperidones by reductive alkylation of an amine using reducing agents such as sodium cyanoborohydride optimally in the presence of a means of promoting Schiff base formation such as with molecular sieves. Furthermore, the N-protected 3-piperidone can be reduced to the alcohol as illustrated in Scheme 18, acylated with a good leaving group like mesylate which in turn is displaced by R^8NH_2 to afford compound 34.

SCHEME 19

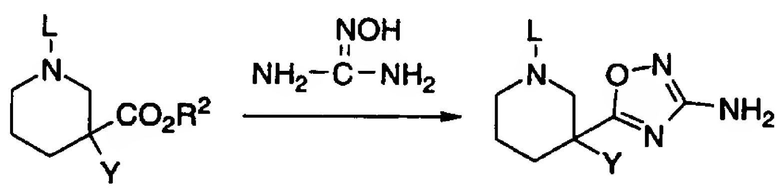


33 35 36

Intermediates of formula 36 may be prepared from mesylate 33 by displacing this group with a sulfide or with potassium thioacetate

followed by oxidation to the sulfonyl chloride using Cl_2. Displacement of the chloride with $HN(R^2)(R^8)$ affords the corresponding sulfonamide 36. If R^2 is hydrogen the sulfonamide may be further alkylated with a strong base such as NaH in DMF followed by an equivalent of an alkyl or arylalkyl halide. Alternatively, the compound 33 may be reacted with sodium sulfite to afford a sulfonic acid that can be reacted with oxalyl chloride or thionyl chloride to give compound 35 which is converted to 36 as outlined in Scheme 19.

SCHEME 20



15a 37

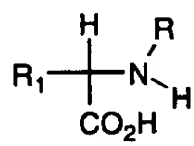
The introduction of hererocycles in the piperidine 3-position from cyano, iminoether, ester, amide and hydroxyamidine substituents in that position is done by methods known in the art. As illustrated in Scheme 20 a 3-amino-1,2,4-oxadiazol-5-yl is synthesized by reacting an ester with hydroxyguanidine in a protic solvent such as ethanol int he presence of sodium ethoxide at reflux. 5-Alkyl-1,2,4-oxadiazol-5-yls are prepared by acylating a protected piperidine 3-hydroxyamidine with an acid chloride in a solvent like pyridine at elevated temperatures.

Compounds of the general formula 2 prepared in this manner are racemic when X and Y are not identical. Resolution of the two enatiomers can be conveniently achieved by classical crystallization methods by using a chiral acid such as L- or D-tartaric acid, (+) or (-)-10-camphorsulfonic acid in a suitable solvent such as acetone, water, alcohol, ether, acetate or their mixture. Alternatively, the racemic amine 2 can be reacted with a chiral auxiliary such as (R) or (S)-O-acetylmandelic acid followed by chromatographic separation of the two diastereomers, and removal of the chiral auxiliary by hydrolysis.

Alternatively asymmetric alkylation can also be utilized for the synthesis of optically active intermediate by introducing a removable chiral auxiliary in X or in place of L with subsequent chromatographic separation of diastereomers.

In cases where a sulfide is present in the molecule, it may be oxidized to a sulfoxide or to a sulfone with oxidizing agents such as sodium periodate, m-chloroperbenzoic acid or Oxone® in an solvent such as dichloromethane, alcohol or water or their mixtures.

The compounds of the present invention may also be prepared from a variety of substituted natural and unnatural amino acids of formulas 46. The preparation of many of these acids is described in US Patent No. 5,206,237. The preparation of these intermediates in racemic form is accomplished by classical methods familiar to those skilled in the art (Williams, R. M. "*Synthesis of Optically Active α-Amino Acids*" Pergamon Press: Oxford, 1989; Vol. 7). Several methods exist to resolve (DL)-

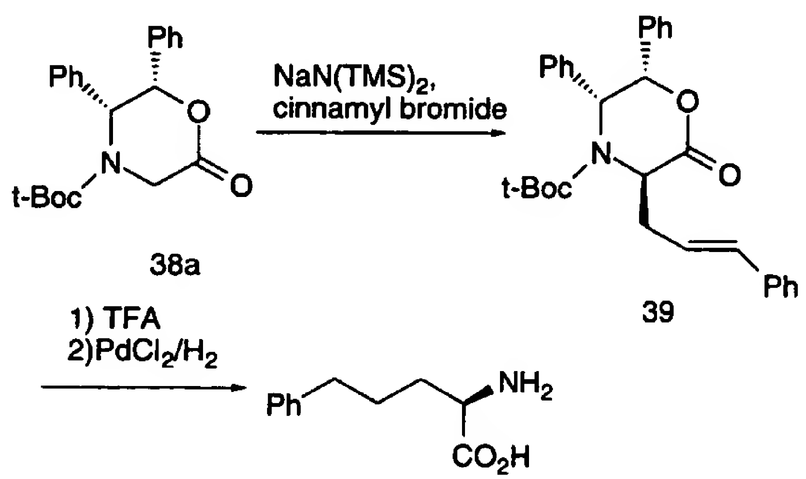


38

amino acids. One of the common methods is to resolve amino or carboxyl protected intermediates by crystallization of salts derived from optically active acids or amines. Alternatively, the amino group of carboxyl protected intermediates may be coupled to optically active acids by using chemistry described earlier. Separation of the individual diastereomers either by chromatographic techniques or by crystallization followed by hydrolysis of the chiral amide furnishes resolved amino acids. Similarly, amino protected intermediates may be converted to a mixture of chiral diastereomeric esters and amides. Separation of the mixture using methods described above and hydrolysis of the individual diastereomers provides (D) and (L) amino acids. Finally, an enzymatic method to resolve N-acetyl derivatives of (DL)-amino acids has been reported by Whitesides and coworkers in *J. Am. Chem. Soc.* 1989, 111, 6354-6364.

When it is desirable to synthesize these intermediates in optically pure form, established methods include: (1) asymmetric electrophilic amination of chiral enolates (*J. Am. Chem. Soc.* 1986, 108, 6394-6395, 6395-6397, and 6397-6399), (2) asymmetric nucleophilic amination of optically active carbonyl derivatives, (*J. Am. Chem. Soc.* 1992, 114, 1906; *Tetrahedron Lett.* 1987, 28, 32), (3) diastereoselective alkylation of chiral glycine enolate synthons (*J. Am. Chem. Soc.* 1991, 113, 9276; *J. Org. Chem.* 1989, 54, 3916), (4) diastereoselective nucleophilic addition to a chiral electrophilic glycinate synthon (*J. Am. Chem. Soc.* 1986, 108, 1103), (5) asymmetric hydrogenation of prochiral dehydroamino acid derivatives ("*Asymmetric Synthesis, Chiral Catalysis*; Morrison, J. D., Ed; Academic Press: Orlando, FL, 1985; Vol 5), and (6) enzymatic syntheses (*Angew. Chem. Int. Ed. Engl.* 1978, *17*, 176).

SCHEME 21



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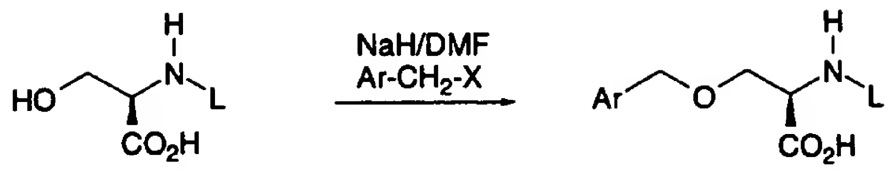
For example, alkylation of the enolate of diphenyloxazinone 38a (*J. Am. Chem. Soc.* 1991, 113, 9276) with cinnamyl bromide in the presence of sodium bis(trimethylsilyl)amide proceeds smoothly to afford 39 which is converted into the desired (D)-2-amino-5-phenylpentanoic acid 40 by removing the N-t-butyloxycarbonyl group with trifluoroacetic acid and hydrogenation over a $PdCl_2$ catalyst (Scheme 21).

SCHEME 22



41 42

Intermediates of formula 42 which are O-benzyl-(D)-serine derivatives 42 are conveniently prepared from suitably substituted benzyl halides and N-protected-(D)-serine 41. The protecting group L is conveniently a BOC or a CBZ group. Benzylation of 41 can be achieved by a number of methods well known in the literature including deprotonation with two equivalents of sodium hydride in an inert solvent such as DMF followed by treatment with one equivalent of a variety of benzyl halides (*Synthesis* 1989, 36) as shown in Scheme 22.

The O-alkyl-(D)-serine derivatives may also be prepared using an alkylation protocol. Other methods that could be utilized to prepare (D)-serine derivatives of formula 42 include the acid catalyzed benzylation of carboxyl protected intermediates derived from 41 with reagents of formula Ar-$CH_2OC(=NH)CCl_3$ (O. Yonemitsu et al., *Chem. Pharm. Bull.* 1988, 36, 4244). Alternatively, alkylation of the chiral gylcine enolates (*J. Am. Chem. Soc.* 1991, *113*, 9276; *J. Org. Chem.* 1989, *54*, 3916) with $ArCH_2OCH_2X$ where X is a leaving group affords 43. In addition D,L-O-aryl(alkyl)serines may be prepared and resolved by methods described above.

It is noted that in some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products.

The utility of the compounds of the present invention as growth hormone secretagogues may be demonstrated by methodology known in the art, such as an assay described by Smith, *et al.*, *Science*, *260*, 1640-1643 (1993) (see text of Figure 2 therein). In particular, the intrinsic growth horomone secretagogue activities of the compounds of

the present invention may be demonstrated in this assay. The compounds of the following examples have activity in the aforementioned assay in the range of 0.1 nm to 5 μm.

The growth hormone releasing compounds of Formula I are useful *in vitro* as unique tools for understanding how growth hormone secretion is regulated at the pituitary level. This includes use in the evaluation of many factors thought or known to influence growth hormone secretion such as age, sex, nutritional factors, glucose, amino acids, fatty acids, as well as fasting and non-fasting states. In addition, the compounds of this invention can be used in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that somatostatin inhibits growth hormone release and that the growth hormone releasing factor (GRF) stimulates its release. Other hormones that are important and in need of study as to their effect on growth hormone release include the gonadal hormones, e.g., testosterone, estradiol, and progesterone; the adrenal hormones, e.g., cortisol and other corticoids, epinephrine and norepinephrine; the pancreatic and gastrointestinal hormones, e.g., insulin, glucagon, gastrin, secretin; the vasoactive peptides, e.g., bombesin, the neurokinins; and the thyroid hormones, e.g., thyroxine and triiodothyronine. The compounds of Formula I can also be employed to investigate the possible negative or positive feedback effects of some of the pituitary hormones, e.g., growth hormone and endorphin peptides, on the pituitary to modify growth hormone release. Of particular scientific importance is the use of these compounds to elucidate the subcellular mechanisms mediating the release of growth hormone.

The compounds of Formula I can be administered to animals, including man, to release growth hormone *in vivo*. For example, the compounds can be administered to commercially important animals such as swine, cattle, sheep and the like to accelerate and increase their rate and extent of growth, to improve feed efficiency and to increase milk production in such animals. In addition, these compounds can be administered to humans *in vivo* as a diagnostic tool to directly determine whether the pituitary is capable of releasing growth hormone. For

example, the compounds of Formula I can be administered *in vivo* to children. Serum samples taken before and after such administration can be assayed for growth hormone. Comparison of the amounts of growth hormone in each of these samples would be a means for directly determining the ability of the patient's pituitary to release growth hormone.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of Formula I in association with a pharmaceutical carrier or diluent. Optionally, the active ingredient of the pharmaceutical compositions can comprise an anabolic agent in addition to at least one of the compounds of Formula I or another composition which exhibits a different activity, e.g., an antibiotic growth permittant or an agent to treat osteoporosis or in combination with a corticosteroid to minimize the catabolic side effects or with other pharmaceutically active materials wherein the combination enhances efficacy and minimizes side effects.

Growth promoting and anabolic agents include, but are not limited to, TRH, diethylstilbesterol, estrogens, β-agonists, theophylline, anabolic steroids, enkephalins, E series prostaglandins, retinoic acid, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox. or peptides disclosed in U.S. Patent No. 4,411,890.

A still further use of the growth hormone secretagogues of this invention is in combination with other growth hormone secretagogues such as the growth hormone releasing peptides GHRP-6, GHRP-1 as described in U.S. Patent Nos. 4,411,890 and publications WO 89/07110, WO 89/07111 and B-HT920 as well as hexarelin and GHRP-2 as described in WO 93/04081 or growth hormone releasing hormone (GHRH, also designated GRF) and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2 or α-adrenergic agonists such as clonidine or serotonin 5HTID agonists such as sumitriptan or agents which inhibit somatostatin or its release such as physostigmine and pyridostigmine. For example, a compound of the present invention may be used in combination with IGF-1 for the

treatment or prevention of obesity. In addition, a compound of this invention may be employed in conjunction with retinoic acid to improve the condition of musculature and skin that results from intrinsic aging.

As is well known to those skilled in the art, the known and potential uses of growth hormone are varied and multitudinous. Thus, the administration of the compounds of this invention for purposes of stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself. These varied uses may be summarized as follows: stimulating growth hormone release in elderly humans; treating growth hormone deficient adults; prevention of catabolic side effects of glucocorticoids; treatment of osteoporosis; stimulation of the immune system, acceleration of wound healing; accelerating bone fracture repair; treatment of growth retardation; treating acute or chronic renal failure or insufficiency; treatment of physiological short stature, including growth hormone deficient children; treating short stature associated with chronic illness; treating obesity and growth retardation associated with obesity; treating growth retardation associated with Prader-Willi syndrome and Turner's syndrome; accelerating the recovery and reducing hospitalization of burn patients or following major surgery such as gastrointestinal surgery; treatment of intrauterine growth retardation, and skeletal dysplasia; treatment of hypercortisonism and Cushing's syndrome; treatment of peripheral neuropathies; replacement of growth hormone in stressed patients; treatment of osteochondrodysplasias, Noonans syndrome, sleep disorders, schizophrenia, depression, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treatment of pulmonary dysfunction and ventilator dependency; prevention or treatment of congestive heart failure, improving pulmonary function, restoring systolic and diastolic function, increasing myocardial contractility, decreasing peripheral total vascular resistance, diminishing or preventing loss of body weight and enhancing recovery following congestive heart failure; increasing appetite; attenuation of protein catabolic response after a major operation; treating malabsorption syndromes; reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; accelerating weight gain and

protein accretion in patients on TPN (total parenteral nutrition); treatment of hyperinsulinemia including nesidioblastosis; adjuvant treatment for ovulation induction and to prevent and treat gastric and duodenal ulcers; stimulation of thymic development and preventtion of the age-related decline of thymic function; adjunctive therapy for patients on chronic hemodialysis; treatment of immunosuppressed patients and to enhance antibody response following vaccination; increasing the total lymphocyte count of a human, in particular, increasing the T4/T8-cell ratio in a human with a depressed T4/T8-cell ratio resulting, for example, from infection, such as bacterial or viral infection, especially infection with the human immunodeficiency virus; treatment of syndromes manifested by non-restorative sleep and musculoskeletal pain, including fibromyalgia syndrome or chronic fatigue syndrome; improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; stimulation of osteoblasts, bone remodelling, and cartilage growth; stimulation of the immune system in companion animals and treatment of disorders of aging in companion animals; growth promotant in livestock; and stimulation of wool growth in sheep. Further, the instant compounds are useful for increasing feed efficiency, promoting growth, increasing milk production and improving the carcass quality of livestock. Likewise, the instant compounds are useful in a method of treatment of diseases or conditions which are benefited by the anabolic effects of enhanced growth hormone levels that comprises the administration of an instant compound.

In particular, the instant compounds are useful in the prevention or treatment of a condition selected from the group consisting of: osteoporosis; catabolic illness; immune deficiency, including that in individuals with a depressed T4/T8 cell ratio; bone fracture, including hip fracture; musculoskeletal impairment in the elderly; growth hormone deficiency in adults or in children; short stature in children; obesity; sleep disorders; cachexia and protein loss due to chronic illness such as AIDS or cancer; and treating patients recovering from major surgery, wounds or burns, in a patient in need thereof.

In addition, the instant compounds may be useful in the treatment of illnesses induced or facilitated by corticotropin releasing factor or stress- and anxiety-related disorders, including stress-induced depression and headache, abdominal bowel syndrome, immune suppression, HIV infections, Alzheimer's disease, gastrointestinal disease, anorexia nervosa, hemorrhagic stress, drug and alcohol withdrawal symptoms, drug addiction, and fertility problems.

It will be known to those skilled in the art that there are numerous compounds now being used in an effort to treat the diseases or therapeutic indications enumerated above. Combinations of these therapeutic agents some of which have also been mentioned above with the growth hormone secretagogues of this invention will bring additional, complementary, and often synergistic properties to enhance the growth promotant, anabolic and desirable properties of these various therapeutic agents. In these combinations, the therapeutic agents and the growth hormone secretagogues of this invention may be independently present in dose ranges from one one-hundredth to one times the dose levels which are effective when these compounds and secretagogues are used singly.

Combined therapy to inhibit bone resorption, prevent osteoporosis and enhance the healing of bone fractures can be illustrated by combinations of bisphosphonates and the growth hormone secretagogues of this invention. The use of bisphosphonates for these utilities has been reviewed, for example, by Hamdy, N.A.T., "Role of Bisphosphonates in Metabolic Bone Diseases" *Trends in Endocrinol. Metab.*, *4*, 19-25 (1993). Bisphosphonates with these utilities include alendronate, tiludronate, dimethyl-APD, risedronate, etidronate, YM-175, clodronate, pamidronate, and BM-210995. According to their potency, oral daily dosage levels of the bisphosphonate of between 0.1 mg and 5 g and daily dosage levels of the growth hormone secretagogues of this invention of between 0.01 mg/kg to 20 mg/kg of body weight are administered to patients to obtain effective treatment of osteoporosis.

In the case of alendronate daily oral dosage levels of 0.1 mg to 50 mg are combined for effective osteoporosis therapy with 0.01

mg/kg to 20 mg/kg of the growth hormone secretagogues of this invention.

Osteoporosis and other bone disorders may also be treated with compounds of this invention in combination with calcitonin, estrogens, raloxifene and calcium supplements such as calcium citrate.

Anabolic effects especially in the treatment of geriatric male patients are obtained with compounds of this invention in combination with anabolic steroids such as oxymetholone, methyltesterone, fluoxymesterone and stanozolol.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and can be formulated in dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl

oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

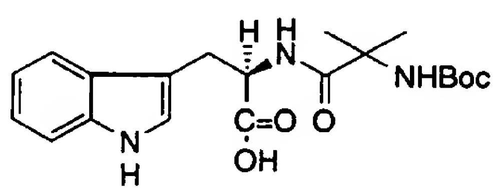
Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

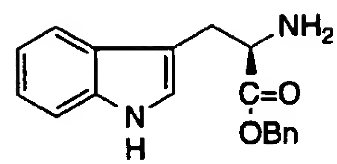
The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 0.0001 to 10 mg/kg. of body weight daily are administered to patients and animals, e.g., mammals, to obtain effective release of growth hormone.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

INTERMEDIATE 1



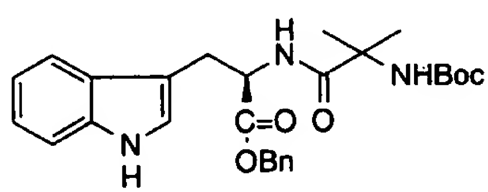
Step A:



To a solution of the commercially available N-t-BOC-D-tryptophan (25.0 g, 82.2 mmol), benzyl alcohol (10.2 mL, 98.6 mmol), and DMAP (100 mg) in dichloromethane (200 mL) at 0°C, was added EDC (17.4 g, 90.4 mmol) in several portions over a one hour period. The reaction mixture was stirred at room temperature for six hours and was poured into water (200 mL), and the organic layer was separated. The organic solution was washed with a mixture of brine and 3 N hydrochloric acid, dried over anhydrous magnesium sulfate, filtered and concentrated to give a thick oil, which solidified upon standing.

To a solution of this oil in 30 mL of dichloromethane was added 20 mL of TFA and stirred for 1h. The reaction mixture was concentrated, neutralized carefully with saturated aqueous sodium bicarbonate solution, and extracted with dichloromethane (2X100 mL). The combined organic solution was washed with brine (100 mL), passed through a short column of silica gel eluting with 5-10% methanol in dichloromethane to give 23.2 g of the amine as an oil after evaporation.

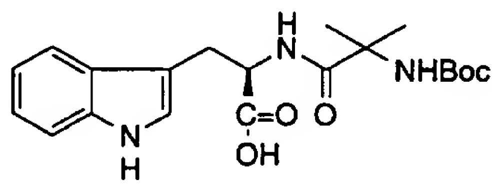
Step B:



To a solution of the above product , HOBT (10.6 g, 78.8 mmol) and N-BOC-α-methyl alanine (19g, 94.5 mmol) in 200 mL of dichloromethane, was added EDC (19.5 g, 0.102 mol) in several portions at 0°C. After 5 minutes, the clear reaction mixture became milky. After stirring at room temperature overnight, the reaction mixture was poured into 200 mL of water and the organic layer was separated. The organic solution was washed with brine, and with a brine and saturated sodium

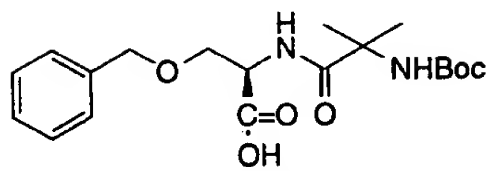
bicarbonate solution, dried over anhydrous magnesium sulfate, filtered and concentrated to give a thick oil, which was purified by flash chromatography eluting with 10-40% ethyl acetate in hexane to give the desired material (28.7 g).
^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.48 (br.s, 1H), 7.54 (br.d, 1H), 7.38-7.23 (m, 3H), 7.19 (br.d, 2H), 7.15-7.00 (m, 1H), 6.90 (d, 1H), 6.86 (d, 1H), 5.06 (br.s, 2H), 4.95 (ddd, 1H), 3.30 (2dd, 2H), 1.40 (s, 15H)

Step C:



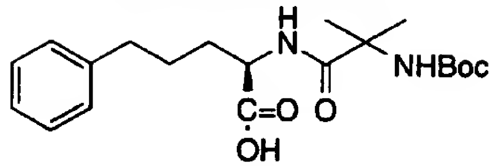
A solution of the material from Step B (28.7g) in 200 mL of ethanol was stirred at RT under a H_2 balloon for 20 minutes in the presence of 10% palladium on carbon (2 g). The catalyst was filtered off through a pad of celite and washed with ethyl acetate. The filtrate was concentrated to give the acid as a slightly pink foam (23.3 g).
^{1}H NMR (CD_3OD, 400 MHz) δ 7.56 (d, J=8 Hz, 1 H), 7.31 (dd, J=1, 8 Hz, 1 H), 7.09 (s, 1 H), 7.07 (dt, J=1, 7 Hz, 1 H), 6.98 (dt, J=1, 7 Hz, 1 H), 4.69 (t, J=6 Hz, 1 H), 3.34-3.23 (m, 2 H), 1.35 (s, 3 H), 1.34 (s, 9 H), 1.29 (s, 3 H).
FAB-MS calc. for $C_{20}H_{27}N_3O_5$: 389 ; Found 390 (M+H), 290 (M+H-100 (BOC))

INTERMEDIATE 2



Following the procedures for the preparation of Intermediate 1 using N-t-Boc-O-Benzyl-D-serine in the place of N-t-BOC-D-tryptophan gave Intermediate 2. FAB-MS calc. for $C_{19}H_{28}N_2O_6$: 380; Found 381 (M+H), 325 (M+H-56 (t-Bu)), 281 (M+H-100 (BOC)).

INTERMEDIATE 3



Step A: (DL)-N-Acetyl-2-amino-5-phenylpentanoic acid

To a solution of sodium (2.3 g, 0.1 mol) in ethanol (60 mL) under nitrogen at room temperature, was added diethyl acetamidomalonate. The mixture was stirred at room temperature for one hour, and then 1-bromo-3-phenylpropane was added dropwisely. After the addition, the mixture was stirred at room temperature for two hours, then refluxed overnight. It was cooled to room temperature and partitioned between water and ethyl acetate. The organic layer was washed with sodium bicarbonate in water, dried over MgSO4 and evaporated to give an intermediate (32.5 g, 97%).

^{1}H NMR (CDCl3, 400MHz) 7.26-7.10 (m, 5 H); 6.75 (br. s, 1 H); 4.19 (q, J=7 Hz, 4 H); 2.58 (t, J=7.9 Hz, 2 H); 2.39-2.35 (m, 2 H); 2.00 (s, 3 H); 1.43-1.39 (m, 2 H); 1.20 (t, J=7 Hz, 6 H).

The product above was suspended in 190 mL of 2.5 N NaOH in water and refluxed for two hours. The mixture was cooled to 0°C, and it was carefully neutralized with 6 N HCl to pH2. The precipitate was collected using a glass sinter funnel and washed with a small amount of cold water and air dried. The solid was then suspended in 300 mL of water and refluxed for four hours. The solution was cooled and acidified to pH1 and the solid was collected by filtration (15.3 g, 67%).

^{1}H NMR (CD3OD, 400MHz) 7.26-7.12 (m, 5 H); 4.90-4.37 (m, 1 H); 2.65-2.60 (m, 2 H); 1.97 (s, 3 H); 1.87 -1.82 (m, 1 H); 1.73-1.65 (m, 3 H).

Step B: (D)-N-Acetyl-2-amino-5-phenylpentanoic acid

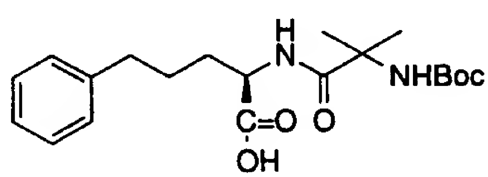
The racemic intermediate from the previous step (10 g, 42.5 mmol) and CoCl3-6H2O were dissolved in 21 ml of 2 N KOH and 200 mL of water at 40°C, and the pH of the solution was adjusted to 8 by the addition of the several drops of 2 N KOH. Then acylase I (Aspergillus sp, 0.5 u/mg, from Sigma; 0.9 g) was added with vigorous stirring. The

reaction mixture was stirred for one day at 40°C and the pH was kept at 8 by the addition of a few drops of KOH. The solid which formed was filtered off. The filtrate was acidified by 3 N HCl to pH2, and was extracted with ethyl acetate (200 mLX4). The organic extracts were combined and evaporated to give a white solid (4.64 g, 46%)
^{1}H NMR (CD3OD, 400MHz) 7.26-7.12 (m, 5 H); 4.90-4.37 (m, 1 H); 2.65-2.60 (m, 2 H); 1.97 (s, 3 H); 1.87 -1.82 (m, 1 H); 1.73-1.65 (m, 3 H).

Step C: (D)-N-t-Boc-2-amino-5-phenylpentanoic acid

The intermediate from step B (4.2 g, 17.8 mmol) was suspended in 2 N HCl (100 mL) and refluxed for two hours. The reaction mixture was evaporated in vacuo to remove water and hydrochloric acid to yield a white solid. To a solution of this solid in 50 mL of water, was added 3 N NaOH until the pH 11, then di-t-butyl dicarbonate (4.66 g, 21.4 mmol) was added with vigorous stirring. After four hours, the reaction mixture was acidified to pH2 with 3 N HCl and it was extracted with ethyl acetate (100 mLX3). The organic extracts were combined and evaporated to give a white solid (6.56 g, crude) which was used without purification. ^{1}H NMR (CD3OD, 400MHz) 7.26-7.12 (m, 5 H); 4.11-4.08 (m, 1 H); 2.65-2.60 (m, 2 H); 1.83-1.62 (m, 4 H); 1.43 (s, 9 H).

Step D:



Following the procedures for the preparation of Intermediate 1 using (D)-N-t-Boc-2-amino-5-phenylpentanoic acid in the place of N-t-BOC-D-tryptophan gave Intermediate 3. ^{1}H NMR ($CDCl_3$, 400MHz) 7.24-7.20 (m, 2H), 7.15-7.04 (m, 3H), 4.60-4.55 (m, 1H), 2.62-2.55 (m, 2H), 2.00-1.86 (m, 1H), 1.78-1.60 (m, 3H), 1.50 (s, 6H), 1.30 (s, 9H).

EXAMPLE 1

N'-Benzyl-N'-phenylsulfonyl-3-amino-piperidine hydrochloride

Step A: N-(*tert* -Butoxycarbonyl)-3-piperidinol

To a solution of 3-piperidinol (2.51 g; 18.2 mmol) in 10% Na_2CO_3 (66 ml) and dioxane (27 ml), cooled to O°C, is added di-*tert* -butyl dicarbonate (3.57 g; 17.1 mmol) portionwise. After the addition, the reaction mixture was stirred for an additional two hours at room temperature. The aqueous phase was extracted with EtOAc (5 x 100 ml). The combined organic extracts were then washed with 10% aqueous citric acid, water, saturated aqueous NaCl, dried ($MgSO_4$), filtered, and evaporated. The compound was dried in vacuo to afford 2.93 g of the title compound which was used in the next step without further purification.

^{1}H-NMR (300 MHz, CD_3OD, ppm): δ 1.03-1.53 (m, 11H), 1.54-1.79 (m, 1H), 1.80-1.95 (m, 1H), 2.53-3.09 (m, 2H), 3.4-3.53 (m, 1H), 3.55-3.72 (m, 1H), 3.73-3.90 (dd, 1H).

Step B: N-(*tert* -Butoxycarbonyl)piperidin-3-one

To a cooled (-65°C) solution of DMSO (1.42 ml; 20 mmol) in CH_2Cl_2 (30ml) was added oxalyl chloride (0.87 ml; 10 mmol). The resulting suspension was stirred for an additional 15 minutes at -65°C, whereupon the product of Step A (2.17 g; 10 mmol) dissolved in 5 ml of CH_2Cl_2 was added portionwise and the reaction was stirred for an additional 15 minutes at that temperature. Triethylamine (5.56 ml; 40 mmol) was then added dropwise, and the solution was allowed to warm to room temperature, whereupon the reaction was stirred for an additional 1.5 hours. The reaction was quenched with H_2O and extracted several times with EtOAc. The combined organic phase was washed with 10% aqueous citric acid, H_2O, saturated aqueous NaCl, dried ($MgSO_4$), filtered and evaporated. The residue was purified on a silica gel flash chromatography column eluted with 25% EtOAc-hexanes. The fractions

containing pure material were combined and concentrated in vacuo to afford 1.87 g of the title compound as a yellow oil.
^{1}H-NMR (400MHz, CD_3OD, ppm): δ 1.38-1.48 (s, 9H), 1.52-1.72 (m, 1H), 1.90-2.00 (p, 1H), 2.40-2.50 (t, 1H), 2.95-3.15 (m, 1H), 3.45-3.80 (m, 3H), 3.90-4.00 (s, 1H).

Step C: N-(*tert* -Butoxycarbonyl)-N-benzyl-3-aminopiperidine

To a solution of the title compound in Step B (500 mg; 2.5 mmol) in MeOH (7 ml) consisting of HOAc (425μl), benzylamine (273μl; 2.5 mmol), and 4 A° powdered sieves, was added $NaCNBH_3$ (319 mg; 5.0 mmol) at room temperature. The reaction was stirred at room temperature for two hours, whereupon it was quenched with H_2O and extracted with EtOAc (2 x 200 ml). The combined organic extracts were washed with 1N aqueous NaOH, H_2O, saturated aqueous NaCl, dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica gel radial chromatography eluted with CH_2Cl_2 followed by CH_2Cl_2-MeOH (20:1). The fractions containing pure material were combined and concentrated in vacuo to afford 601 mg of the title compound as a yellow oil. The material was used as is in the next step.

Step D: N-(*tert* -Butoxycarbonyl)-N-benzyl-N'-phenylsulfonyl-3-aminopiperidine

To a solution of the title compound in Step C (601 mg; 2.07 mmol) in CH_2Cl_2 (2 ml) and N-methylmorpholine (227 μl; 2.07 mmol), cooled to O°C, was added phenylsulphonylchloride (396 μl; 3.1 mmol), and the reaction was allowed to stir at room temperature for three hours. The reaction was quenched with H_2O and extracted with EtOAc. The organic phase was washed with H_2O, saturated aqueous NaCl, dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica gel radial chromatography eluted with CH_2Cl_2. The fractions containing pure material were combined and concentrated in vacuo to afford 468 mg of the title compound as a white foam.
^{1}H-NMR (300 MHz, CD_3OD, ppm): δ 1.20-1.40 (s, 9H), 1.45-1.65 (m, 4H), 2.20-2.60 (m, 2H), 3.45-3.70 (bs, 1H), 3.75-3.93 (dd, 2H), 4.25-4.45

(d, 1H), 4.50-4.4.65 (d, 1H), 7.10-7.43 (m, 5H), 7.45-7.70(m, 3H), 7.75-7.90 (dd, 2H). CI-MS *m/e* = 431 (M+1).

Step E: N'-benzyl-N'-phenylsulfonyl-3-amino-piperidine hydrochloride

A solution of the title compound in Step D (264 mg; 0.613 mmol) in cold saturated solution of HCl in THF (2 ml) was stirred at room temperarure for one hour. The solvent was removed in vacuo and the residue was triturated with EtOAc, filtered under N_2, washed with EtOAc, ether, and let dry under vacuo and N_2. The solid was dried in vacuo overnight to yield 206 mg of the title compound as a white solid. ^{1}H-NMR (300 MHz, CD_3OD, ppm): δ 1.40-1.95 (m, 4H), 2.46-2.75 (t, 2H), 2.94-3.20 (m, 2H), 3.82-4.10 (m, 1H), 4.18-4.44 (d, 1H), 4.49-4.74 (d, 1H), 7.05-7.45 (m, 5H), 7.50-7.75 (m, 3H), 7.80-8.00 (dd, 2H). CI-MS *m/e* = 331 (M+1).

EXAMPLE 2

N-Phenyl-N'-phenylsulfonyl-3-amino-piperidine hydrochloride

Step A: N-(*tert* -Butoxycarbonyl)-N-phenyl-3-aminopiperidine

The titled compound was prepared from the product obtained in Step B of Example 1, using a procedure similar to that described in Step C of Example 1 replacing benzylamine with aniline as the amine source. Purification yields 522 mg (60%) of the title compound as a yellow solid, which was used as is in the next step.

Step B: N-(*tert* -Butoxycarbonyl)-N-phenyl-N'-phenylsulfonyl-3-aminopiperidine

The titled product was prepared from the product obtained in Step A using the procedure in Step D of Example 1 to yield 530 mg (67%) of the titled compound as a white solid.
^{1}H-NMR (300 MHz, CD_3OD, ppm): δ 1.03-1.32 (m, 1H), 1.35-1.55 (s, 9H), 1.55-1.70 (m, 2H), 2.15-2.60 (m, 2H), 3.70-3.94 (d, 1H), 3.97-4.16

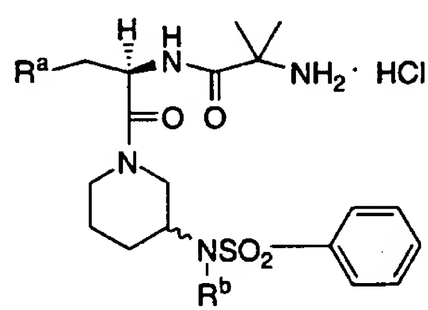
(m, 1H), 4.17-4.30 (d, 1H), 6.85-7.03 (dd, 2H), 7.20-7.43 (m, 3H), 7.45-7.80 (m, 5H). CI-MS *m/e* = 418 (M+1).

Step C: N-phenyl-N'-phenylsulfonyl-3-aminopiperidine hydrochloride

The titled product was prepared from the product obtained in Step B using the procedure described in Step E of Example 1 to yield 403 mg of the titled compound as a white solid.

^{1}H-NMR (300 MHz, CD_3OD, ppm): δ 1.15-1.40 (m, 1H), 1.70-2.05 (m, 3H), 2.55-2.65 (dd, 1H), 2.66-2.80 (t, 1H), 3.15-3.25 (dd, 1H), 3.45-3.60 (dd, 1H), 4.40-4.60 (m, 1H), 6.92-7.11 (dd, 2H), 7.18-7.45 (m, 3H), 7.47-7.80 (m, 5H). CI-MS *m/e* = 318 (M+1).

EXAMPLE 3



The following general synthesis was applied for the preparation of all compounds listed in Table I below:

Step A:

A solution of the Intermediate 1 (or 3) (0.268 mmol) in CH_2Cl_2 (1 ml) was cooled to 0°C, to which was added the titled compound from Step E of Example 1 (or Step C of Example 2) (0.314 mmol). To the solution was then added HOBT (0.392 mmol), followed by NMM (0.527 mmol), and EDC (0.344 mmol). The reaction was stirred for one hour at room temperature, and then partitioned between H_2O and EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$, H_2O, 10% aqueous citric acid, H_2O, saturated aqueous NaCl,

dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica gel radial chromatography eluted with 50% EtOAc-hexanes. The fractions containing pure compound were combined and concentrated in vacuo to afford the desired product as either a mixture of diastereoismers (1+2), or individual isomers (1 or 2).

Step B:

HCl(g) was bubbled into a solution of the product from Step A (0.108 mmol) in EtOAc (2 ml), and the reaction was stirrred at room temperature for one hour. The solvent was removed in vacuo, and the residue was triturated with ether, filtered under N_2, and dried in vacuo to yield the desired product as a white solid.

TABLE I

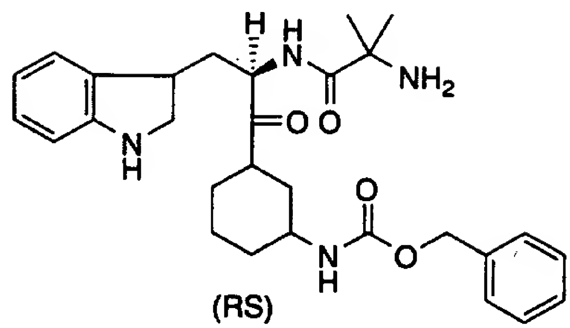
Isomer	R^a	R^b	CI-MS (M+1)	Log P (min)	Cpd #
Recemic	3-Indolyl	$-CH_2Ph$	602	3.6	3a
Isomer 1	3-Indolyl	Ph	588	3.2	3b
Isomer 2	3-Indolyl	Ph	588	3.0	3c
Isomer 1	$Ph(CH_2)_3$-	$-CH_2Ph$	591	4.4	3d
Isomer 2	$Ph(CH_2)_3$-	$-CH_2Ph$	591	4.4	3e
Recemic	$Ph(CH_2)_3$-	Ph	577	4.2	3f
Isomer 2	$Ph(CH_2)_3$-	Ph	577	4.0	3g

TABLE II

Cpd #	^{1}H-NMR δ (400 MHz, CD_3OD, ppm)
3a	-0.433-(-)0.151(m, 0.22H), 0.795-1.84 (m, 11H), 1.89-2.08(m, 1.2H), 2.09-2.25 (m, 0.37H), 2.35-2.57 (m, 0.33H), 2.67-2.89 (m, 0.26H), 2.94-3.26 (m, 2.4H), 3.46-3.78 (m, 1.45H), 3.79-3.95 (m, 0.39H), 4.00-4.38 (m, 2.57H), 4.44-4.62 (m, 0.53H), 4.64-4.83 (m, 0.41H), 4.94-5.17 (m, 1.3H), 6.75-8.07 (m, 15H).

3b	0.78-0.98 (m, 0.4H), 1.02-1.26 (m, 1.3H), 1.30-1.76 (m, 8.8H), 1.77-2.01 (m, 2.0H), 2.06-2.29 (m, 0.45H), 2.76-2.99 (m, 0.41H), 3.00-3.25 (m, 1.9H), 3.34-3.81 (m, 1.8H) 3.97-4.15 (m, 0.7H), 4.19-4.34 (m, 0.5H), 4.37-4.51 (m, 0.4H), 4.53-4.51 (m, 0.6H), 4.98-5.29 (m, 1.1H), 6.76-7.91 (m, 15H).
3c	-0.229-0.093 (m, 0.11H), 0.854-1.13 (m, 1.25H), 1.16-1.95 (m, 10.9H), 1.98-2.19 (m, 0.25H), 2.34-2.52 (m, 0.19H), 2.98-3.27 (m, 2.7H), 3.49-3.69 (m, 0.51H), 4.11-4.36 (m, 1.47H), 4.53-4.70 (m, 0.2H), 4.92-5.19 (m, 1.24H), 6.24-6.49 (m, 1.3H), 6.77-6.98 (m, 1.9H), 7.00-7.49 (m, 6.49H), 7.51-7.98 (m, 5.29H).
3d	0.736-1.06 (m, 0.15H), 1.11-2.02 (m, 16.3H), 2.09-2.41 (m, 1.1H), 2.46-2.84 (m, 3.62), 2.86-3.03 (m, 2.1H), 3.05-3.27 (1.1H), 3.38-3.56 (m, 0.49H), 3.60-3.80 (m, 1.3H), 3.85-4.07 (m, 0.7H), 4.08-4.19 (m, 0.3H), 4.22-4.49 (m, 2.1H), 4.50-4.86 (m, 1.6H), 6.98-7.50 (m, 9.9H), 7.51-7.72 (m, 2.9H), 7.74-8.03 (m, 2.22H).
3e	0.864-1.07 (m, 0.3H), 1.09-2.00 (m, 16H), 2.13-2.38 (m, 0.9H), 2.46-2.88 (m, 3.6H), 3.04-3.26 (m, 0.5H), 3.43-3.78 (m, 1.3H), 3.87-4.07 (m, 0.8H), 4.09-4.19 (m, 0.3H), 4.21-4.50 (m, 2.2H), 4.52-4.78 (m, 1.9H), 7.03-7.50 (m, 9.9H), 7.51-7.56 (m, 3.1H), 7.78-7.93 (m, 1.1H), 7.95-8.12 (m, 0.9H).
3f	1.02-1.49 (m, 2H), 1.52-2.13 (m, 14H), 2.16-2.43 (m, 1H), 2.48-2.93 (m, 3.3H), 2.96-3.13 (m, 0.3H), 3.15-3.25 (m, 0.2H), 3.43-3.83 (m, 0.8H), 3.90-4.74 (m, 3H), 4.74-4.84 (m, 0.5H), 4.92-5.01 (m, 0.4H), 6.87-8.04(m, 15H).
3g	0.991-2.06 (m, 16.7H), 2.14-2.38 (m, 0.8H), 2.49-2.95 (m, 2.5H), 3.47-3.72 (m, 0.55H), 3.89-4.21 (m, 1H), 4.23-4.46 (m, 1.2H), 4.48-4.58 (m, 0.2H), 4.59-4.70 (0.37H), 4.72-4.82 (m, 0.5H), 6.86-8.04 (15H).

EXAMPLE 4



Step A: Racemic N-(*tert* -Butoxycarbonyl)-3-(N'-[carbobenzoxy])-piperidine

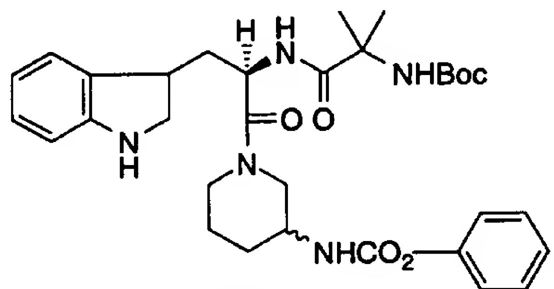
To a solution of racemic N-Boc nipecotic acid (230 mg; 1 mmol]) in toluene (12 ml) under nitrogen was added diphenylphosphoryl azide (DPPA) (259 μl; 1.2 mmol) and triethylamine (TEA) (170 μl; 1.22 mmol). The reaction was refluxed under nitrogen for one hour. The solvent was removed in vacuo, CH_2Cl_2 (20 ml) and THF (20 ml) were added to the residue, followed by benzyl alcohol (115 μl; 1.5 mmol) and DMAP (122 mg; 1 mmol). The solution was refluxed overnight, and then concentrated in vacuo to yield a residue which was partitioned between H_2O and EtOAc. The aqueous phase was extracted once more EtOAc, and the combined organic extracts was washed with 10% aqueous $NaHCO_3$, H_2O, 10% aqueous citric acid, H_2O, saturated aqueous NaCl, dried ($MgSO_4$), filtered and evaporated. The crude oil was purified by silica gel radial chromatography eluted with EtOAc-hexanes (25:75) to yield150 mg of the titled compound.
^{1}H-NMR (300 MHz, CD_3OD, ppm): δ 1.3-1.5 (s, 11H), 1.61-2.15 (m, 3H), 2.19-2.58 (m, 2H), 2.67-2.87 (m, 1H), 2.91-3.11 (m, 1H), 3.31-3.60 (m, 1H), 5.17 (s, 2H), 7.00-7.60 (m, 5H).

Step B: Racemic 3-(N-Carbobenzoxy])piperidine hydrochloride

The titled compound was prepared from the product obtained in Step A using a procedure similar to that of Step E in Example 1. Purification yields 115 mg of the titled compound as a white solid.

^{1}H-NMR (300 MHz, CD_3OD, ppm): δ 1.09-2.72 (m, 3H), 1.76-1.99 (m, 1H), 2.18-2.59 (m, 2H), 2.67-2.87 (m, 1H), 2.91-3.11 (m, 1H), 3.31-3.60 (m, 1H), 4.89-5.17 (s, 2H), 7.00-7.60 (m, 5H). CI-MS *m/e* : 235 (M+1).

Step C:



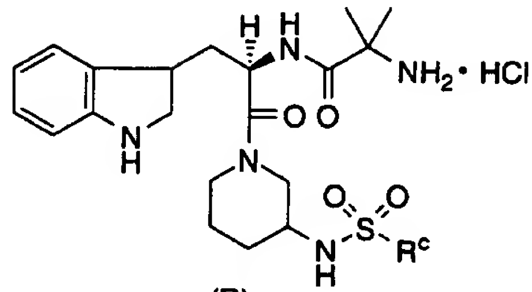
(RS)

The product of Step B was coupled with Intermediate 1 as decribed in Step A of Example 3 to provide the desired compound (a mixture of diastereoisomer) as a white solid.
^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.736-0.991 (m, 4H), 1.04-1.89 (m, 24H), 2.21-2.42 (m, 0.7H), 2.50-2.80 (m, 1.4H), 2.84-3.25 (m, 3.7H), 3.30-3.78 (m, 3H), 3.96-4.22 (m, 0.7H), 4.95-5.33 (m, 3.7H), 6.84-7.73 (m, 10H). ESI-MS *m/e* : 606 (M+1).

Step D:

The compound (50 mg) obtained in Step C was dissolved in dry ethylacetate (1ml) saturated with HCl(g) at room temperature. The mixture was stirred at that temperature for 1 h. The product was precepitated from the reaction with dry ether and filtered. The title compound was obtained as a hydrochloride salt (white solid). Yield 35 mg. ^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.74-0.96 (m, 4H), 1.0-1.89 (m, 15H), 2.21-2.42 (m, 0.7H), 2.50-2.80 (m, 1.4H), 2.84-3.25 (m, 3.7H), 3.30-3.78 (m, 3H), 3.96-4.22 (m, 0.7H), 4.95-5.33 (m, 3.7H), 6.84-7.73 (m, 10H). ESI-MS *m/e* : 506 (M+1).

EXAMPLE 5



(R)

Step A: N-(*tert*-Butoxycarbonyl)-(R)-nipecotic acid.

To solution of racemic N-Boc-nipecotic acid (15 g) in ethylacetate (500 ml) was slowly added (S)-α-methyl benzylamine (12. 25 ml) at room temperature, and stirring continued at that temperature for 1h. The precepitate formed was filtered, washed with ethylacetate (30 ml) and dried (10g), and then crystallized from ethylacetate containing 10% methanol. The crystallized material was filtered, washed with ethyl acetate and dried. Yield: 7.6 g; mp: 176-178°C. The ethyl acetate suspension of the salt was treated with aqueous 10 % citric acid. The organic phase was then washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to provide the pure R-acid as a white solid (5.1 mg). mp: 168-169°C; $[\alpha]_D = +48.3^o$ (c=1, MeOH).

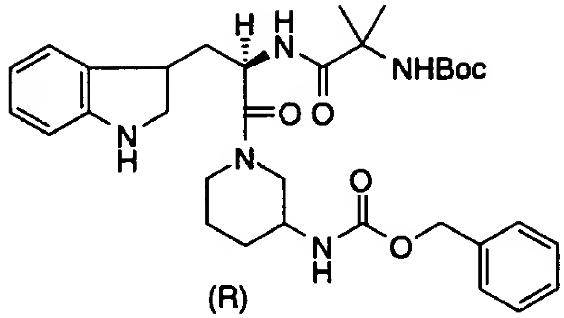
Step B: 3-(R)-(N-Carbobenzoxyl)piperidine hydrochloride

The titled compound was prepared from the product (230 mg) obtained in Step A using a procedure similar to that described in Steps A and B of Example 4. Purification yields 115 mg of the titled compound as a white solid.

^{1}H-NMR (300 MHz, CD_3OD, ppm): δ 1.09-2.72 (m, 3H), 1.76-1.99 (m, 1H), 2.18-2.59 (m, 2H), 2.67-2.87 (m, 1H), 2.91-3.11 (m, 1H), 3.31-3.60 (m, 1H), 4.89-5.17 (s, 2H), 7.00-7.60 (m, 5H).

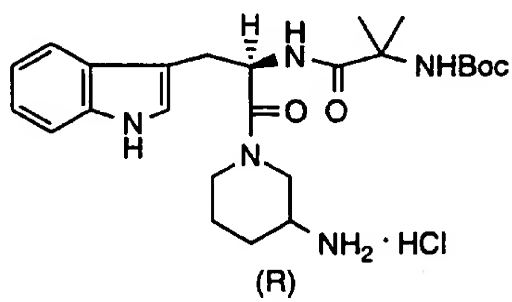
CI-MS *m/e* : 235 (M+1).

Step C:



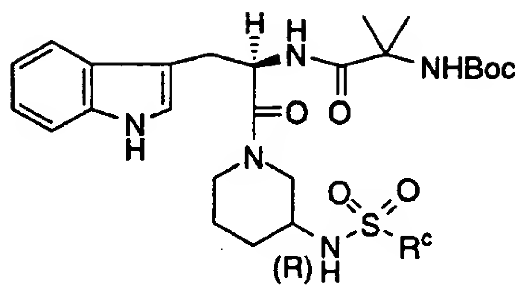
The above compound was prepared from the product of Step B using the procedure described in Step C of Example 4. ^{1}H-NMR (400 MHz, CD_3OD, ppm): δ 0.736-0.991 (m, 0.4H), 1.04-1.89 (m, 24H), 2.21-2.42 (m, 0.7H), 2.50-2.80 (m, 1.4H), 2.84-3.25 (m, 3.7H), 3.30-3.78 (m, 3H), 3.96-4.22 (m, 0.7H), 4.95-5.33 (m, 3.7H), 6.84-7.73 (m, 10H). ESI-MS *m/e* : 606 (M+1).

Step D:



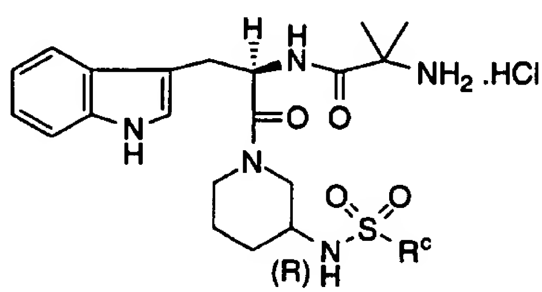
To a solution of the titled compounds in Step C (320 mg; 0.531 mmol) in MeOH (10 ml) and $CHCl_3$ (200 µl), was added Pd/C (46 mg), and the mixture was stirred in an atmosphere of H_2 for two days. The mixture was then filtered through a pad of celite, and the filtrate was concentrated in vacuo to yield 260 mg of the titled compound. ^{1}H-NMR (300 MHz, CD_3OD, ppm): δ 0.053-0.404 (m, 0.15H), 1.02-1.81 (m, 20H), 1.85-2.07 (m, 0.4H), 2.11-2.46 (m, 1H), 2.74-3.21 (m, 4H), 3.78-4.11 (m, 0.7H), 4.21-4.43 (m, 0.2H), 4.92-5.20 (m, 1H), 6.81-7.96 (m, 5H).

Step E:



The product from Step D was reacted with appropriate sulfonyl chlorides, using the conditions described in Step D of Example 1, to provide the desired protected sulfonamides. The compounds were purified by silica-gel radial chromatography using EtOAc-hexanes (66:33) to yield the title compounds as a white solid.

Step F:



The compounds prepared in Step E were deprotected with HCl/EtOAc, as described in Step B of Example 2, to provide titled compounds (Tables III and IV).

The corresponding S-isomers (described in Tables III & IV) were made similarly starting with N-(*tert* -butoxycarbonyl)-(S)-nipecotic acid.

N-(*tert* -butoxycarbonyl)-(S)-nipecotic acid was prepared from racemic N-BOC-neipecotic acid using (R)-α-methylbenzyl amine as the resolving agent as described in Step A.

mp. 170-171°C; $[\alpha]_D = -48.6^{\circ}$ (c =1, MeOH).

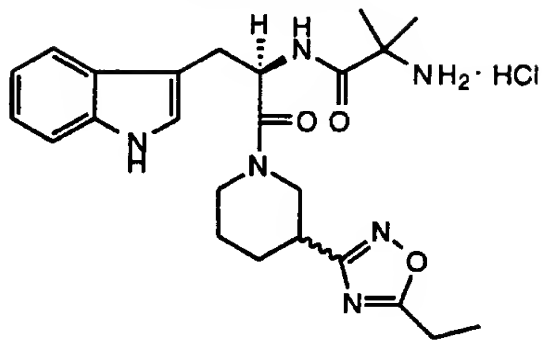
TABLE III

Isomer	Cpd #	R^c	CI-MS(M^+)	Mol. formula
R	5a	Ph	512	$C_{26}H_{33}N_5SO_4$
S	5b	Ph	512	$C_{26}H_{33}N_5SO_4$
R	5c	quinol-8-yl	563	$C_{29}H_{34}N_6SO_4$
S	5d	quinol-8-yl	563	$C_{29}H_{34}N_6SO_4$

TABLE IV

Cpd #	^{1}H-NMRδ (400 MHz, CD_3OD, ppm)
5a	0.834-1.92 (m, 11H), 2.14-2.51 (m, 1H), 2.69-3.25 (m, 5H), 3.46-3.70 (m, 0.7H), 4.00-4.44 (m, 0.7H), 4.69-4.84 (m, 0.7H), 4.99-5.25 (m, 0.6H), 6.82-8.03 (m, 10H), 8.09-8.47 (0.3H).
5b	-0.102-0.147 (m, 0.12H), 0.806-1.90 (m, 10H), 2.07-2.35 (m, 0.9H), 2.38-2.64 (m, 0.8H), 2.67-2.91 (m, 0.5H), 2.98-3.25 (m, 2.5H), 3.58-3.84 (m, 0.46H), 4.01-4.32 (m, 0.85H), 4.99-5.26 (m, 0.77H), 6.85-8.03 (m, 10H), 8.08-8.37 (m, 0.3H).
5c	0.785-1.83 (m, 13H), 2.39-2.68 (m, 0.9H), 2.78-3.27 (m, 4.5H), 3.88-4.12 (m, 0.6H), 4.99-5.22 (m, 0.5H), 6.69-7.56 (m, 5H), 7.66-8.11 (m, 2H), 8.18-8.67 (m, 2H), 8.70-8.87 (m, 0.5H), 8.89-9.12 (m, 0.9H), 9.16-9.39 (m, 0.4H).
5d	-0.10-0.305 (m, 0.1H), 0.803-1.798 (m, 11H), 2.37-3.25 (m, 4.2H), 3.37-4.00 (m, 1.3H), 4.97-5.19 (m, 0.6H), 6.69-7.61 (m, 5H), 7.68-8.11 (m, 2H), 8.16-8.77 (m, 2.3H), 8.79-9.05 (0.9H), 9.07-9.36 (m, 0.9H).

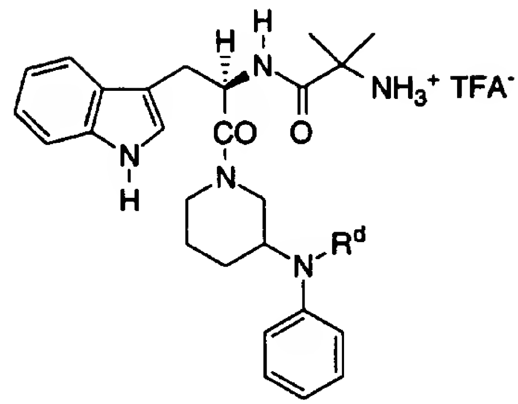
EXAMPLE 6



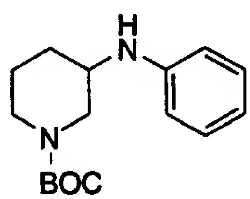
(diastereomeric mixture)

To a solution of 20mg of Intermediate 1, 0.020mL of N-methylmorpholine, 20mg of EDC and 20mg of HOBT in 2mL of CH_2Cl_2 was added 11mg of 3-(5-ethyl-1,2,4-oxadiazolyl)piperidine hydrochloride and stirred for a day at room temperature (the piperidine hydrochloride was prepared in 3 steps from N-t-BOC protected 3-cyanopiperidine by a) addition of hydroxylamine to the nitrile in refluxing methanol, b) acylation of the amino-oxime with propionylchloride in pyridine, and c) deprotection of the N-t-BOC protecting group with HCl (gas) in ethyl acetate). The reaction mixture was poured into 5mL of CH_2Cl_2 and washed with (2X3mL) of 0.50N HCl solution, 3mL of 1N aqueous sodium hydroxide solution, dried over anhydrous magnesium sulfate, filtered and concentrated to give a thick oil. Flash chromatography of this material (10g silica gel; hexane:acetone (5:1) as the eluent) gave 13.6mg of the coupled product as a diastereomeric mixture. This material was deprotected by treating an EtOAc solution with dry HCl (gas) for 5 min. Ether was added and the precipitate was collected under nitrogen and dried. The title compound was a white to off-white solid. FAB-MS *m/e* : 453.59 (M+1).

EXAMPLE 7

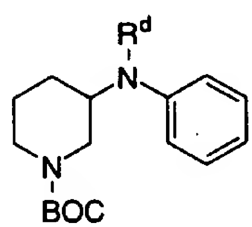


Step A:



The title compound was prepared by the methodology of Example 2, Step A.

Step B:

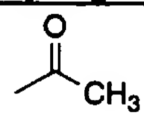
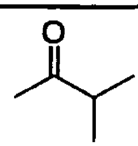
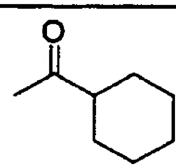
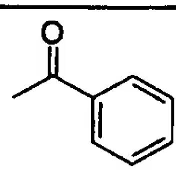


To a solution of the amine from Step A (300 mg; 1.1 mmol) in CH_2Cl_2 (5.0 mL) was added triethylamine (1.5 mL; 10.8 mmol), DMAP (catalytic) and acetic anhydride (0.5 mL; 5.4 mmol). The mixture was refluxed until complete by TLC analysis whereupon the reaction was diluted with ethyl acetate, washed with 2N HCl, saturated potassium carbonate, water, brine, dried (K_2CO_3) and concentrated. Radial

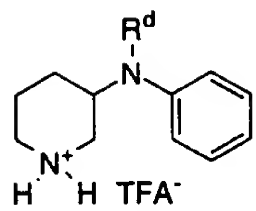
chromatography (2mm plate; 4;1 hexanes:ethyl acetate) of the residue gave the compounds of Table V.

The sulfonamides of Table V (7B-6 to 9) were prepared essentially in the manner described in Example 1, Step D using known sulfonyl chlorides.

TABLE V

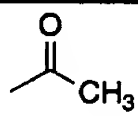
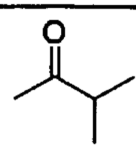
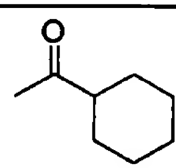
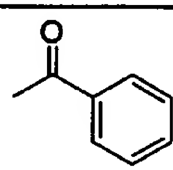
Example #	R^d	Mass Spectral Data
7B-1	hydrogen	-
7B-2		218.2 (MH^+ - CO_2-t-Bu)
7B-3		247.2 (MH^+ - CO_2-t-Bu)
7B-4		287.3 (MH^+ - CO_2-t-Bu)
7B-5		281.2 (MH^+ - CO_2-t-Bu)
7B-6	$-SO_2CH_3$	255 (MH^+ - CO_2-t-Bu)
7B-7	$-SO_2Ph$	-
7B-8	$-SO_2CH(CH_3)_2$	283 (MH^+ - CO_2-t-Bu)
7B-9	$-SO_2$-t-Bu	297 (MH^+ - CO_2-t-Bu)
7B-10	$-C(O)NH_2$	(ND)
7B-11	$-C(O)NHCH_3$	(ND)
7B-12	$-C(O)NHCH(CH_3)_2$	(ND)
7B-13	-C(O)NHPh	(ND)

Step C:

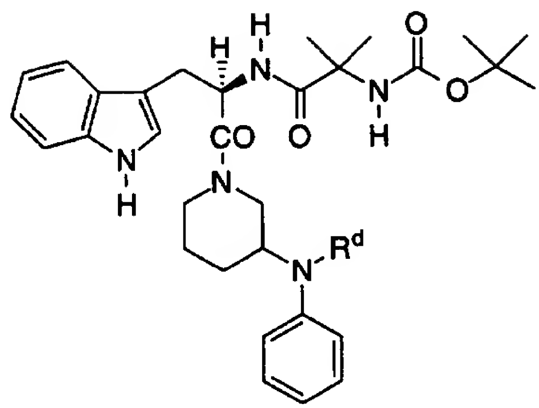


The appropriate N-BOC derivatives were deprotected in the general manner described herein with trifluoroacetic acid in dichloromethane at 0°C to give the amine salts of Table VI.

TABLE VI

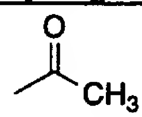
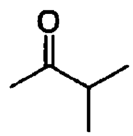
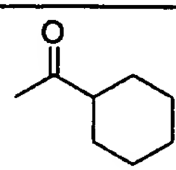
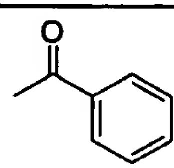
Example #	R^d	Mass Spectral Data
7C-1	hydrogen	-
7C-2		219.2 (MH^+)
7C-3		246.33 (MH^+)
7C-4		287.3 (MH^+)
7C-5		281.2 (MH^+)
7C-6	$-SO_2CH_3$	255 (MH^+)
7C-7	$-SO_2Ph$	-
7C-8	$-SO_2CH(CH_3)_2$	283 (MH^+)
7C-9	$-SO_2$-t-Bu	297 (MH^+)
7C-10	$-C(O)NH_2$	(ND)
7C-11	$-C(O)NHCH_3$	(ND)
7C-12	$-C(O)NHCH(CH_3)_2$	(ND)
7C-13	-C(O)NHPh	(ND)

Step D:

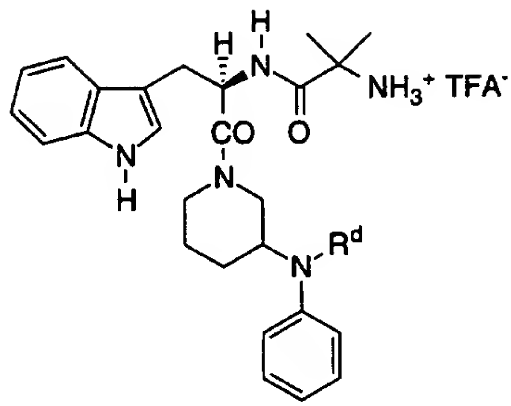


To a solution of the appropriate amine salt (1 equivalent) from Step C in dichloromethane was added N-methyl morpholine (1 equivalent) and the mixture was stirred 10 minutes. To this mixture was added d-TRP-BocAIB (1 equivalent), HOBT (1 equivalent) and EDCI (2 equivalents). The reaction was stirred until complete by TLC analysis whereupon the reaction was worked up in the general manner described herein and the chromatographed in the general manner described herein to give the compounds of Table VII.

TABLE VII

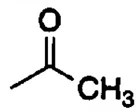
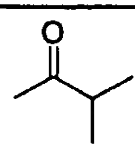
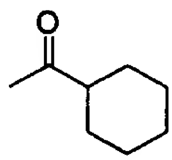
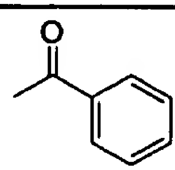
Example #	R^d	Mass Spectral Data
7D-1	hydrogen	548.3 (MH^+)
7D-2		514.7 (MH^+ - O-t-Bu)
7D-3		544.3 (MH^+ - O-t-Bu)
7D-4		584.4(MH^+ - O-t-Bu)
7D-5		578.3 (MH^+ - O-t-Bu)
7D-6	$-SO_2CH_3$	526 (MH^+ - CO_2-t-Bu)
7D-7	$-SO_2Ph$	-
7D-8	$-SO_2CH(CH_3)_2$	554 (MH^+ - CO_2-t-Bu)
7D-9	$-SO_2$-t-Bu	568 (MH^+ - CO_2-t-Bu)
7D-10	$-C(O)NH_2$	(ND)
7D-11	$-C(O)NHCH_3$	(ND)
7D-12	$-C(O)NHCH(CH_3)_2$	(ND)
7D-13	-C(O)NHPh	(ND)

Step E:



The appropriate N-BOC derivatives from Step D were deprotected in the general manner described herein with trifluoroacetic acid in dichloromethane at 0°C to give the amine salts of Table VIII.

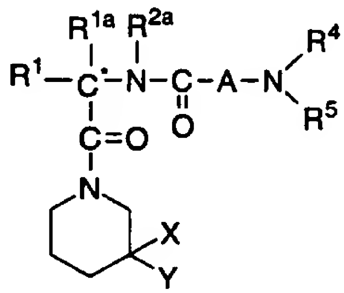
TABLE VIII

Example #	R^d	Mass Spectral Data
7E-1	hydrogen	448.3 (MH^+)
7E-2		-
7E-3		518.2 (MH^+)
7E-4		558.3 (MH^+)
7E-5		552.3 (MH^+)
7E-6	$-SO_2CH_3$	526 (MH^+)
7E-7	$-SO_2Ph$	-
7E-8	$-SO_2CH(CH_3)_2$	554 (MH^+)
7E-9	$-SO_2$-t-Bu	568 (MH^+)
7E-10	$-C(O)NH_2$	(ND)
7E-11	$-C(O)NHCH_3$	(ND)
7E-12	$-C(O)NHCH(CH_3)_2$	(ND)
7E-13	-C(O)NHPh	(ND)

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of the formula:



Formula I

wherein:

R^1 is selected from the group consisting of:
C_1-C_{10} alkyl, aryl, aryl(C_1-C_6 alkyl), (C_3-C_7 cycloalkyl)(C_1-C_6 alkyl)-, (C_1-C_5 alkyl)-K-(C_1-C_5 alkyl)-, aryl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-, and (C_3-C_7 cycloalkyl)(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-, where K is -O-, -$S(O)_m$-, -$N(R^2)C(O)$-, -$C(O)N(R^2)$-, -OC(O)-, -C(O)O-, -CR^2=CR^2-, or -C≡C-, where aryl is selected from: phenyl, naphthyl, indolyl, azaindole, pyridyl, benzothienyl, benzofuranyl, thiazolyl, and benzimidazolyl, and R^2 and alkyl may be further substituted by 1 to 9 halogen, $S(O)_mR^{2a}$, 1 to 3 of OR^{2a} or $C(O)OR^{2a}$, and aryl may be further substituted by 1 to 3 of C_1-C_6 alkyl, 1 to 3 of halogen, 1 to 2 of -OR^2, methylenedioxy, -$S(O)_mR^2$, 1 to 2 of -CF_3, -OCF_3, nitro, -$N(R^2)C(O)(R^2)$, -$C(O)OR^2$, -$C(O)N(R^2)(R^2)$, -1H-tetrazol-5-yl, -$SO_2N(R^2)(R^2)$, -$N(R^2)SO_2$ phenyl, or -$N(R^2)SO_2R^2$;

R^{1a} is selected from hydrogen and C_1-C_6 alkyl;

R^2 is selected from: hydrogen, C_1-C_6 alkyl, and C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring, optionally including oxygen, sulfur or NR^{3a}, where R^{3a} is hydrogen, or C_1-C_6 alkyl, optionally substituted by hydroxyl;

R^{2a} is selected from hydrogen and C_1-C_6 alkyl;

R^4 and R^5 are independently hydrogen, C_1-C_6 alkyl, or substituted C_1-C_6 alkyl where the substituents are selected from: 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenyloxy, 2-furyl, C_1-C_6 alkoxycarbonyl, $S(O)_m(C_1$-C_6 alkyl), or R^4 and R^5 may be taken together to form $-(CH_2)_d-L_a(CH_2)_e-$ where L_a is $-C(R^2)_2-$, -O-, $-S(O)_m-$ or $-N(R^2)-$, d and e are independently 1 to 3 and R^2 is as defined above;

X is selected from the group consisting of:
$-(CH_2)_qN(R^8)C(O)R^2$, $-(CH_2)_qN(R^8)C(O)R^8$,
$-(CH_2)_qN(R^8)C(O)OR^2$, $-(CH_2)_qN(R^8)C(O)OR^8$,
$-(CH_2)_qN(R^8)C(O)OR^2$, $-(CH_2)_qN(R^2)C(O)OR^8$,
$-(CH_2)_qN(R^8)C(O)OR^8$, $-(CH_2)_qN(R^2)SO_2R^9$, $-(CH_2)_qN(R^8)SO_2R^8$,
$-(CH_2)_qN(R^8)SO_2R^2$,
$-(CH_2)_qN(R^2)SO_2N(R^2)(R^8)$, $-(CH_2)_qN(R^8)C(O)N(R^2)(R^2)$,
$-(CH_2)_qN(R^8)C(O)N(R^2)(R^8)$, $-(CH_2)_qSO_2N(R^2)(R^2)$,
$-(CH_2)_qSO_2N(R^2)(R^8)$, $-(CH_2)_qN(R^2)(R^8)$, and $-(CH_2)_qR^{10}$,
where the R^2 and $(CH_2)_q$ groups may be optionally substituted by 1 to 2 C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, $CONH_2$, $S(O)_mCH_3$, carboxylate C_1-C_4 alkyl esters, or 1H-tetrazol-5-yl;

Y is selected from the group consisting of: hydrogen, C_1-C_{10} alkyl, -$(CH_2)_t$aryl, -$(CH_2)_q$(C_3-C_7 cycloalkyl), -$(CH_2)_q$-K-(C_1-C_6 alkyl), -$(CH_2)_q$-K-$(CH_2)_t$aryl, -$(CH_2)_q$-K-$(CH_2)_t$(C_3-C_7 cycloalkyl containing -O-, -NR^2-, or -S-), and -$(CH_2)_q$-K-$(CH_2)_t$(C_3-C_7 cycloalkyl), where K is as defined above, and where the alkyl, R^2, $(CH_2)_q$ and $(CH_2)_t$ groups may be optionally substituted by C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, -$CONH_2$ or carboxylate C_1-C_4 alkyl esters, and where aryl is phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiopheneyl, quinolinyl, pyrazinyl, or isothiazolyl which is optionally substituted by 1 to 3 halogen, 1 to 3 -OR^2, -C(O)OR^2, -C(O)N(R^2)(R^2), nitro, cyano, benzyl, 1 to 3 C_1-C_4 alkyl, -S(O)$_m$$R^2$, or 1H-tetrazol-5-yl;

A is:

$$-(CH_2)_x-\underset{R^{7a}}{\overset{R^{7}}{\underset{|}{\overset{|}{C}}}}-(CH_2)_y- \qquad \text{or} \qquad -Z-(CH_2)_x-\underset{R^{7a}}{\overset{R^{7}}{\underset{|}{\overset{|}{C}}}}-(CH_2)_y-$$

where x and y are independently 0, 1, 2 or 3;

Z is -N(R^{6a})- or -O-, where R^{6a} is hydrogen or C_1-C_6 alkyl;

R^7 and R^{7a} are independently hydrogen, C_1-C_6 alkyl, trifluoromethyl, phenyl, or substituted C_1-C_6 alkyl where the substituents are imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, -OR^2, -S(O)$_m$$R^2$, -C(O)$OR^2$, C_3-C_7 cycloalkyl, -N(R^2)(R^2), -C(O)N(R^2)(R^2), or R^7 and R^{7a} may independently be joined to one or both of R^4 and R^5 groups to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R^7 or R^{7a} groups, wherein the bridge contains 1 to 5 carbons atoms, or R^7 and R^{7a} can be joined to one another to form C_3-C_7 cycloalkyl;

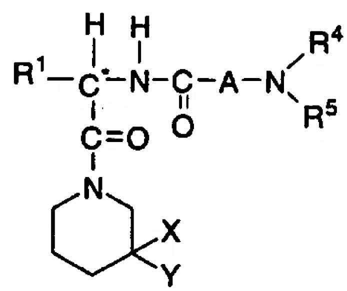
R^8 is $-(CH_2)_p$aryl, where aryl is selected from: phenyl, naphthyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, thienyl, pyrazinyl, pyrimidinyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, indolyl, quinolinyl, and isoquinolinyl, and where the aryl is optionally substituted with 1 to 2 of halogen, $-R^2$, $-OR^2$, $-N(R^2)(R^2)$, $-C(O)OR^2$, or $-C(O)N(R^2)(R^2)$;

R^9 is selected from the group consisting of: isoxazolyl, thiazolyl, isothiazolyl, thienyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, indolyl, quinolinyl, and isoquinolinyl, which are optionally substituted by 1 to 2 of halogen, $-R^2$, $-OR^2$, $-N(R^2)(R^2)$, $-C(O)OR^2$, or $-C(O)N(R^2)(R^2)$;

R^{10} is selected from the group consisting of: 1,2,4-oxadiazolyl, pyrazinyl, triazolyl, and phthalimidoyl, which are optionally substituted with $-R^2$, $-OR^2$ or $-N(R^2)(R^2)$;

m is 0, 1, or 2;
p is 0, 1, 2, or 3;
q is 0, 1, 2, 3, or 4;
t is 0, 1, 2, or 3;
and pharmaceutically acceptable salts and individual diastereomers thereof.

2. The compound of Claim 1 of the formula:



Formula Ia

wherein:

R^1 is selected from the group consisting of: C_1-C_{10} alkyl, aryl (C_1-C_4 alkyl)-, C_3-C_6 cycloalkyl (C_1-C_4 alkyl)-, (C_1-C_4 alkyl)-K-(C_1-C_2 alkyl)-, aryl (C_0-C_2 alkyl)-K-(C_1-C_2 alkyl)-, and (C_3-C_7 cycloalkyl)(C_0-C_2 alkyl)-K-(C_1-C_2 alkyl)-, where K is -O-, -$S(O)_m$-, -OC(O)-, or -C(O)O-, and the alkyl groups may be further substituted by 1 to 7 halogen, -$S(O)_mR^2$, 1 to 3 -OR^2 or -$C(O)OR^2$, and aryl is phenyl, naphthyl, indolyl, pyridyl, benzimidazolyl, azaindolyl, benzothienyl or benzofuranyl which may be further substituted by 1-2 C_1-C_4 alkyl, 1 to 2 halogen, 1 to 2 -OR^2, -$S(O)_mR^2$, or -$C(O)OR^2$;

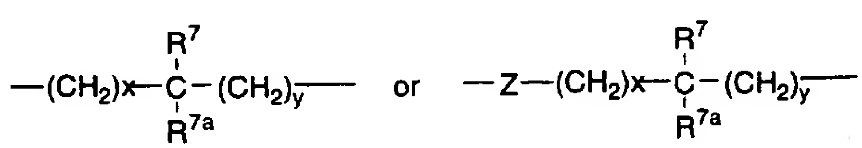
R^2 is hydrogen, C_1-C_6 alkyl, or C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom they may be optionally joined to form a C_4-C_7 cyclic ring optionally including oxygen, sulfur or NR^{3a};

R^4 and R^5 are independently hydrogen, C_1-C_6 alkyl, or substituted C_1-C_6 alkyl where the substituents are 1 to 5 halo, 1 to 3 hydroxyl, -S(O)m (C_1-C_6 alkyl) or phenyl;

X is selected from the group consisting of:
$-(CH_2)_qN(R^8)C(O)R^2$, $-(CH_2)_qN(R^8)C(O)R^8$, $-(CH_2)_qN(R^8)C(O)OR^2$, $-(CH_2)_qN(R^8)C(O)OR^8$, $-(CH_2)_qN(R^8)C(O)OR^2$, $-(CH_2)_qN(R^2)C(O)OR^8$, $-(CH_2)_qN(R^8)C(O)OR^8$, $-(CH_2)_qN(R^2)SO_2R^9$, $-(CH_2)_qN(R^8)SO_2R^8$, $-(CH_2)_qN(R^8)SO_2R^2$, $-(CH_2)_qN(R^2)SO_2N(R^2)(R^8)$, $-(CH_2)_qN(R^8)C(O)N(R^2)(R^2)$, $-(CH_2)_qN(R^8)C(O)N(R^2)(R^8)$, $-(CH_2)_qSO_2N(R^2)(R^2)$, $-(CH_2)_qSO_2N(R^2)(R^8)$, $-(CH_2)_qN(R^2)(R^8)$, and $-(CH_2)_qR^{10}$, where the R^2, and $(CH_2)_q$ groups are optionally substituted by 1 to 2 C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, $CONH_2$, $S(O)_mCH_3$, carboxylate C_1-C_4 alkyl esters, or 1H-tetrazol-5-yl;

Y is selected from the group consisting of:
hydrogen, C_1-C_8 alkyl, $(CH_2)_t$aryl, $-(CH_2)_q(C_5$-C_6 cycloalkyl), $-(CH_2)_q$-K-(C_1-C_6 alkyl), $-(CH_2)_q$-K-$(CH_2)_t$aryl, $-(CH_2)_q$-K-$(CH_2)_t$(C_3-C_7 cycloalkyl containing -O-, $-NR^2$-, or -S-), and $-(CH_2)_q$-K-$(CH_2)_t$ (C_5-C_6 cycloalkyl), where K is -O- or $-S(O)_m$- and where the alkyl groups are optionally substituted by hydroxyl, carboxyl, $CONH_2$, carboxylate C_1-C_4 alkyl esters or 1H-tetrazole-5-yl and aryl is phenyl, naphthyl, pyridyl, 1-H-tetrazolyl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, or thiopheneyl which is optionally substituted by 1 to 3 halogen, 1 to 3 $-OR^2$, $-C(O)OR^2$, $-C(O)N(R^2)(R^2)$, cyano, 1 to 2 C_1-C_4 alkyl, benzyl, $-S(O)_mR^2$, or 1H-tetrazol-5-yl-;

A is:



where x and y are independently 0, 1 or 2;

Z is $-NR^{6a}-$ or -O-, where R^{6a} is hydrogen or C_1-C_3 alkyl;

R^7 and R^{7a} are independently hydrogen C_1-C_6 alkyl, trifluoromethyl, phenyl, substituted C_1-C_6 alkyl where the substituents are imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, OR^2, $S(O)mR^2$, $C(O)OR^2$, C_5-C_7 cycloalkyl, $-N(R^2)(R^2)$, $-C(O)N(R^2)(R^2)$; or R^7 and R^{7a} can independently be joined to one of R^4 or R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portion of R^7 or R^{7a} groups to form 5 or 6 membered rings; or R^7 and R^{7a} can be joined to one another to form a C_3 cycloalkyl;

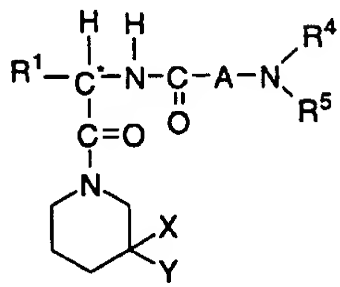
R^8 is $-(CH_2)_p$aryl, where aryl is selected from: phenyl, naphthyl, pyridyl, thiazolyl, isothiazolyl, oxaxolyl, isoxazolyl, thienyl, pyrazinyl, pyrimidinyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, indolyl, quinolinyl, and isoquinolinyl, and where aryl may be substituted by 1 to 2 of halogen, $-R^2$, $-OR^2$, $-N(R^2)(R^2)$, $-C(O)OR^2$, or $-C(O)N(R^2)(R^2)$;

R^9 is selected from the group consisting of: isoxazolyl, thiazolyl, isothiazolyl, thienyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, indolyl, quinolinyl, and isoquinolinyl, which may be substituted by 1 to 2 of halogen, $-R^2$, $-OR^2$, $-N(R^2)(R^2)$, $-C(O)OR^2$, or $-C(O)N(R^2)(R^2)$;

R^{10} is selected from the group consisting of:
1,2,4-oxadiazolyl, pyrazinyl, triazolyl, and phthalimidoyl, which are optionally substituted with $-R^2$, $-OR^2$ or $-N(R^2)(R^2)$;

m is 0, 1 or 2;
p is 0, 1 or 2;
q is 0, 1 or 2;
t is 0, 1 or 2;
and pharmaceutically acceptable salts and individual diastereomers thereof.

3. The compound of Claim 1 of the formula:



Formula 1b

wherein:

R^1 is selected from the group consisting of: C_1-C_{10} alkyl, aryl (C_1-C_3 alkyl)-, (C_3-C_7 cycloalkyl)(C_1-C_3 alkyl)-, and aryl (C_0-C_1 alkyl)-K-(C_1-C_2 alkyl)-, where K is O or $S(O)_m$ and the aryl is phenyl, pyridyl, naphthyl, indolyl, azaindolyl, benzothienyl, or benzimidazolyl which is optionally substituted by 1-2 C_1-C_4 alkyl, 1 to 2 halogen, 1 to 2 -OR^2, -$S(O)_mR^2$, or $C(O)OR^2$;

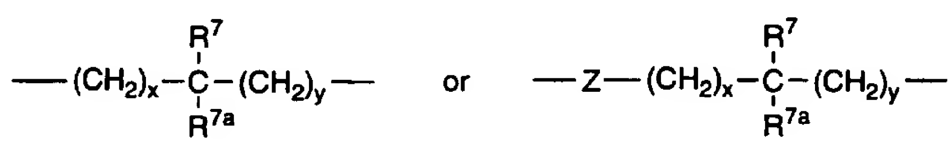
R^2 is hydrogen, C_1-C_6 alkyl, or C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom they may be optionally joined to form a C_5-C_7 cyclic ring optionally including oxygen, sulfur or NR^{3a};

R^4 and R^5 are independently hydrogen, C_1-C_4 alkyl, or substituted C_1-C_3 alkyl where the substituents may be 1 to 2 hydroxyl;

X is selected from the group consisting of:
$-(CH_2)_qN(R^8)C(O)R^2$, $-(CH_2)_qN(R^8)C(O)R^8$,
$-(CH_2)_qN(R^8)C(O)OR^2$, $-(CH_2)_qN(R^8)C(O)OR^8$,
$-(CH_2)_qN(R^8)C(O)OR^2$, $-(CH_2)_qN(R^8)C(O)OR^8$,
$-(CH_2)_qN(R^2)SO_2R^9$, $-(CH_2)_qN(R^8)SO_2R^8$, $(CH_2)qN(R^8)SO_2R^2$,
$-(CH_2)_qN(R^8)C(O)N(R^2)(R^2)$, $-(CH_2)_qN(R^8)C(O)N(R^2)(R^8)$,
$-(CH_2)qSO_2N(R^2)(R^2)$, $-(CH_2)qSO_2N(R^2)(R^8)$,
$-(CH_2)_qN(R^2)(R^8)$, and $-(CH_2)_qR^{10}$,
where the R^2, and $(CH_2)_q$ groups may be optionally substituted by 1 to 2 C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, $-CONH_2$, $-S(O)_mCH_3$, carboxylate C_1-C_4 alkyl esters, or 1H-tetrazol-5-yl;

Y is selected from the group consisting of:
hydrogen, C_1-C_8 alkyl, $(CH_2)_t$aryl, $-(CH_2)q$ C_5-C_7 cycloalkyl, $-(CH_2)q$-K-(C_1-C_6 alkyl), $-(CH_2)q$-K-$(CH_2)_t$aryl, and $-(CH_2)q$-K-$(CH_2)_t$ (C_5-C_6 cycloalkyl), where K is $S(O)_m$ and where the alkyl groups may be optionally substituted by hydroxyl, carboxyl, $CONH_2$, carboxylate C_1-C_4 alkyl esters or 1H-tetrazole-5-yl and aryl is phenyl, naphthyl, indolyl, pyridyl, thiazolyl, thiopheneyl, pyrazolyl, oxazolyl, isoxazolyl or imidazolyl which may be optionally substituted by 1 to 2 halogen, 1 to 2 $-OR^2$, 1 to 2 $-N(R^2)(R^2)$, $-CO(OR^2)$, 1 to 2 C_1-C_4 alkyl, $-S(O)_mR^2$, or 1H-tetrazol-5-yl;

A is:



where x and y are independantly 0 or 1;
Z is $-N(R^{6a})-$ or $-O-$, where R^{6a} is hydrogen or C_1-C_3 alkyl;

R^7 and R^{7a} are independently hydrogen, C_1-C_6 alkyl, phenyl, substituted C_1-C_6 alkyl wherein the substitutent is imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, -OR^2, -$S(O)_mR^2$, or R^7 and R^{7a} can independently be joined to one of R^4 or R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portions of R^7 or R^{7a} groups to form 5 or 6 membered rings; or R^7 or R^{7a} can be joined to one another to form a C_3-C_6 cycloalkyl;

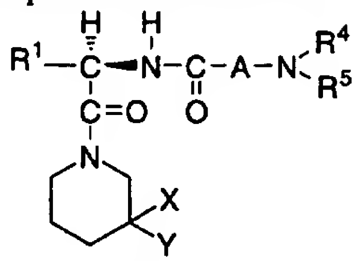
R^8 is -$(CH_2)_p$aryl, where aryl is selected from: phenyl, naphthyl, pyridyl, thiazolyl, isothiazolyl, oxaxolyl, isoxazolyl, thienyl, pyrazinyl, pyrimidinyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, indolyl, quinolinyl, and isoquinolinyl, and where aryl may be substituted by 1 to 2 of halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, or -$C(O)N(R^2)(R^2)$;

R^9 is selected from the group consisting of: isoxazolyl, thiazolyl, isothiazolyl, indolyl, thienyl, benzothienyl, benzofuranyl, benzimidazolyl, imidazolyl, quinolinyl, and isoquinolinyl, which may be substituted by 1 to 2 of halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$, or -$C(O)N(R^2)(R^2)$;

R^{10} is selected form the group consisting of:
1,2,4-oxadiazolyl, pyrazinyl, and triazolyl which may be substituted by -R^2, -OR^2, or -$N(R^2)(R^2)$;

m is 0, 1, or 2;
p is 0, 1, or 2
q is 0, 1,or 2;
t is 0, 1, or 2;
and pharmaceutically acceptable salts and individual diastereomers thereof.

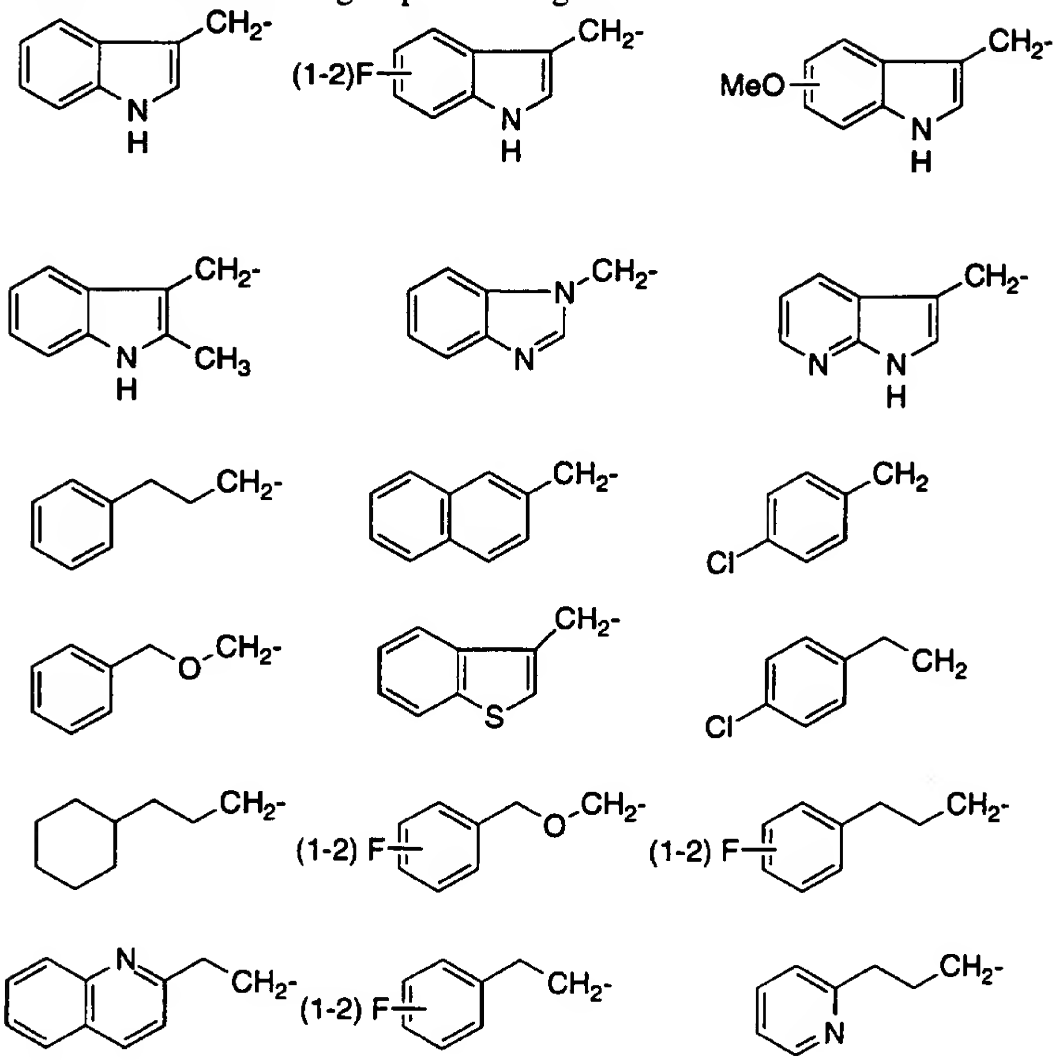
4. A compound of the formula:



Formula Ic

wherein:

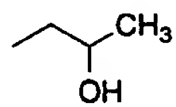
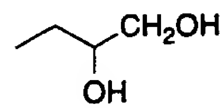
R^1 is selected from the group consisting of:



or their regioisomers where not specified;

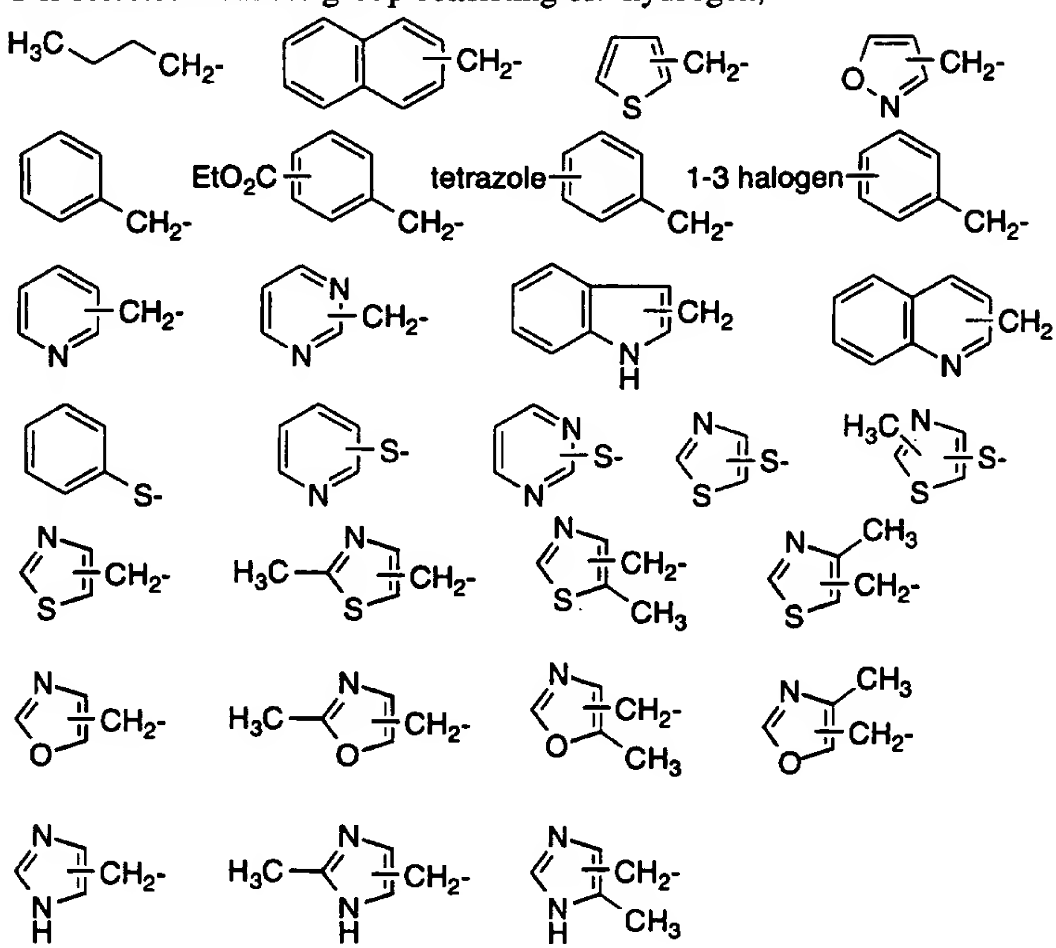
R^2 is hydrogen, C_1-C_6 alkyl, or C_3-C_7 cycloalkyl and where two C_1-C_6 alkyl groups are present on one atom they may be optionally joined to form a C_5-C_7 cyclic ring optionally including oxygen, sulfur or NR^{3a};

R^4 and R^5 are independently selected from the group consisting of:

—H —CH_3 —CH_2CH_3  

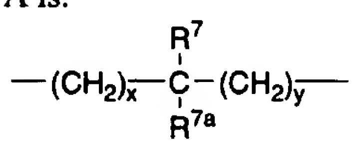
X is selected from the group consisting of:
$-(CH_2)_qN(R^8)C(O)R^2$, $-(CH_2)_qN(R^8)C(O)R^8$,
$-(CH_2)_qN(R^8)C(O)OR^2$, $-(CH_2)_qN(R^2)C(O)OR^8$,
$-(CH_2)_qN(R^8)C(O)OR^8$, $-(CH_2)_qN(R^2)SO_2R^9$,
$-(CH_2)_qN(R^8)SO_2R^8$, $-(CH_2)_qN(R^8)SO_2R^2$,
$-(CH_2)_qN(R^2)SO_2N(R^2)(R^8)$, $-(CH_2)_qN(R^8)C(O)N(R^2)(R^2)$,
$-(CH_2)_qN(R^8)C(O)N(R^2)(R^8)$, and $-(CH_2)_qN(R^2)(R^8)$;

Y is selected from the group consisting of: hydrogen,

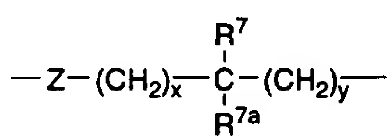


or their regioisomers whereof where not specified;

A is:



or



where x and y are independently 0 or 1;

Z is -(NR^{6a})- or -O-, where R^{6a} is hydrogen or C_1-C_6 alkyl;

R^7 and R^{7a} are independently C_1-C_6 alkyl and substituted C_1-C_6 alkyl wherein the substituent is phenyl, naphthyl or indolyl or R^7 and R^{7a} can independently be joined to one of the R^4 or R^5 to form alkylene bridges between the terminal nitrogen and the alkyl portions of R^7 or R^{7a} to form 5 or 6 membered rings;

R^8 is $(CH_2)_p$aryl where aryl is selected from: phenyl, naphthyl, pyridyl, pyrazinyl, pyrimidinyl, thiazolyl, indolyl, quinolinyl and isoquinolinyl and where the aryl may be substituted by 1 to 2 halogen, -R^2, -OR^2, $N(R^2)(R^2)$, -$C(O)OR^2$ or -$C(O)N(R^2)(R^2)$;

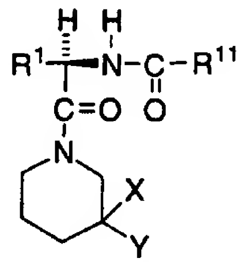
R^9 is selected from the group consisting of: isoxazolyl, thiazolyl, indolyl, quinolinyl and isoquinolinyl, which may be substituted by 1 to 2 halogen, -R^2, -OR^2, -$N(R^2)(R^2)$, -$C(O)OR^2$ or -$C(O)N(R^2)(R^2)$;

R^{10} is 1,2,4-oxadiazolyl which may be substituted by -R^2, -OR^2, or -$N(R^2)(R^2)$;

m is 0, 1 or 2;
p is 0 or 1;
q is 0 or 1;
t is 0 or 1;

and pharmaceutically acceptable salts and individual diasteromers thereof.

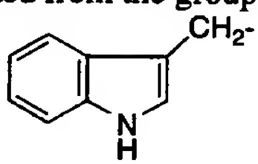
5. A compound of the formula:

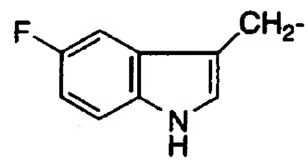


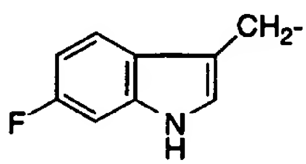
Formula Id

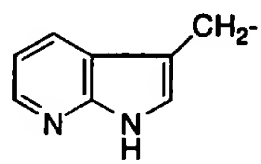
wherein:

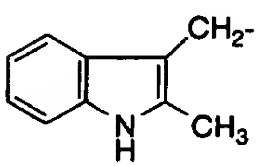
R^1 is selected from the group consisting of:

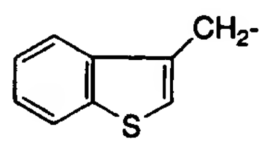




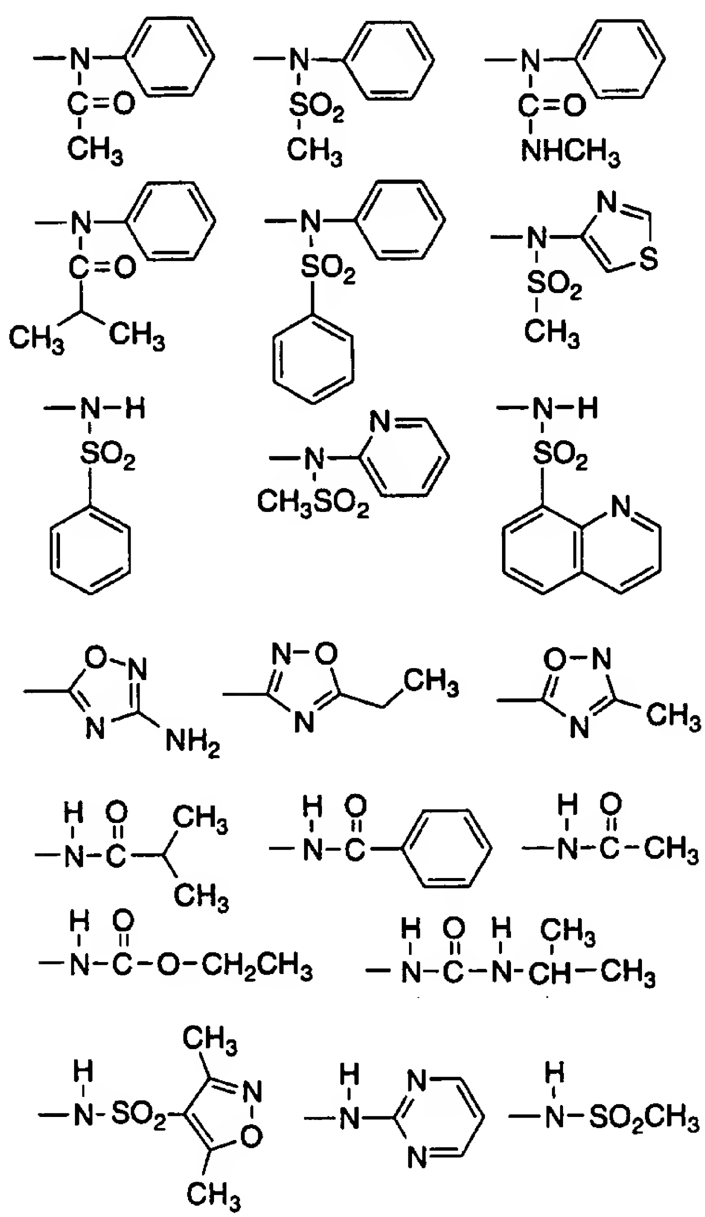




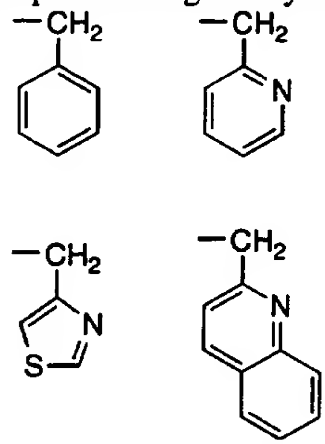




X is selected from the group consisting of:

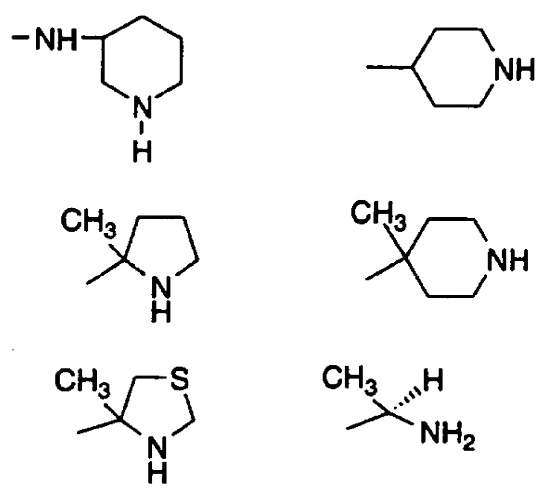


Y is selected from the group consisting of: hydrogen,



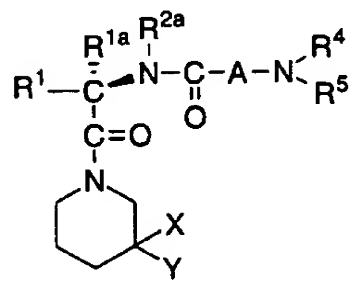
R^{11} is selected from the group consisting of:

$-CH_2C(CH_3)_2NH_2$ $-C(CH_3)_2NH_2$



and pharmaceutically acceptable salts and individual diasteromers thereof.

6. The stereospecifically defined compound of Claim 1 of the formula:



wherein R^1, R^{1a}, R^{2a}, R^4, R^5, A, X, and Y are as defined in Claim 1.

7. A pharmaceutical composition which comprises an inert carrier and an effective amount of a compound of Claim 1.

8. A pharmaceutical composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of a compound of Claim 1 in combination with an additional growth hormone secretagogue.

9. A pharmaceutical composition useful for the treatment of osteoporosis which comprises a combination of a bisphosphonate compound and the compound of Claim 1.

10. The pharmaceutical composition of Claim 9 wherein the bisphosphonate compound is alendronate.

11. A method for increasing levels of endogenous growth hormone in a human or an animal which comprises administering to such human or animal an effective amount of the compound of Claim 1.

12. A method for increasing levels of endogenous growth hormone in a human or an animal which comprises administering to such human or animal an effective amount of the compound of Claim 1 in combination with an additional growth hormone secretagogue.

13. The method of Claim 12 wherein the additional growth hormone secretagogue is selected from the group consisting of: growth hormone releasing factor; an analog of growth hormone releasing factor; IGF-1; and IGF-2.

14. A method for increasing feed efficiency, promoting growth, increasing milk production and improving the carcass quality of livestock which comprises administering to such livestock an effective amount of the compound of Claim 1.

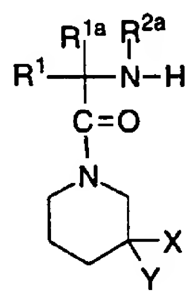
15. A method for the treatment of a disease or a condition which is benefited by the anabolic effects of enhanced growth hormone levels that comprises administering to a patient in need thereof an effective amount the compound of Claim 1.

16. The method of Claim 15 wherein the disease or condition is selected from the group consisting of: osteoporosis; catabolic illness; immune deficiency, including that in individuals with a depressed T4/T8 cell ratio; bone fracture; musculoskeletal impairment in the elderly; growth hormone deficiency in adults or in children; short stature in children; obesity; sleep disorders; cachexia and protein loss due to chronic illness such as AIDS or cancer; and the treatment of patients recovering from major surgery, wounds or burns.

17. A method for the treatment of osteoporosis which comprises administering to a patient with osteoporosis a combination of a bisphosphonate compound and the compound of Claim 1.

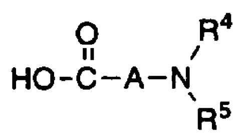
18. The method of Claim 19 wherein the bisphosphonate compound is alendronate.

19. A process for the preparation of a compound of Claim 1 which comprises reacting a compound having the formula:



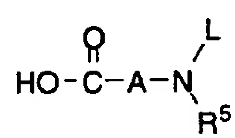
4

with a compound having the formula:



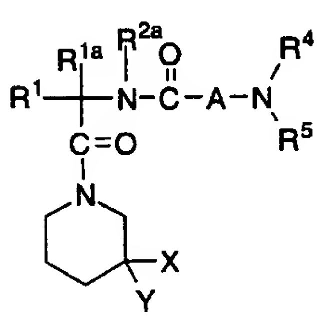
5

or



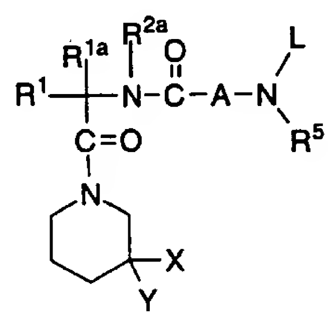
6

to give a compound having the formula:



I

or

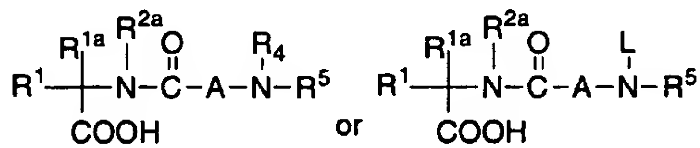


7

;

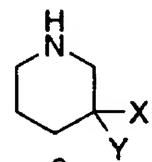
wherein R^1, R^{1a}, R^{2a}, R^4, R^5, A, X, and Y are as defined in Claim 1 and L is a protecting group which is subsequently removed if present and salts are formed if desired.

20. A process for the preparation of a compound of Claim 1 which comprises reacting a compound having the formula:



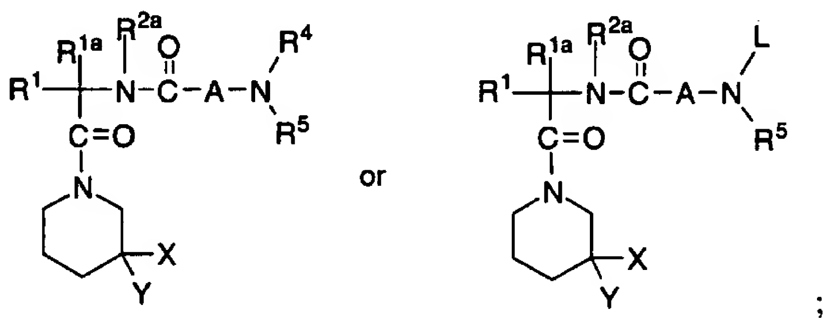
12 or 12a

with a compound having the formula:



2

to give a compound having the formula:



I or 7

wherein R^1, R^{1a}, R^{2a}, R^4, R^5, A, X, and Y are as defined in Claim 1 and L is a protecting group which is subsequently removed if present and salts are formed if desired.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/05254

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS, DIALOG, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, A	US 5,492,916 A (MORRIELLO et al.) 20 February 1996, see whole document and claims 1-10.	1-11, 15, 16, 19
P, A	US 5,494,919 A (MORRIELLO et al.) 27 February 1996, see whole document and claims 1-7.	1-11, 15, 16, 19
P, A	US 5,492,920 (CHEN et al.) 20 February 1996, see whole document and claims 1-8	1-11, 15, 16, 19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 JULY 1996	27 AUG 1996

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	CELIA CHANG
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/05254

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-11, 15, 16, 19

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☒ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/05254

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/445
C07D 401/06; 209/04; 211/56

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/256, 318, 319, 322, 323, 324, 326
544/335
546/193, 199, 201, 202, 205, 209, 210

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

514/256, 318, 319, 322, 323, 324, 326
544/335
546/193, 199, 201, 202, 205, 209, 210

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-10, 11 and 19 drawn to compounds, compositions, method of using compounds for increasing endogenous growth hormone, and first process of making (reacting acylamides with amino acids).

Group II, claims 12-13, drawn to method of increasing growth hormone by combination of chemical compounds together with growth hormone secretage.

Group III, claim 14, drawn to method of increasing feed efficiency.

Group IV, claims 15-16, drawn to method of treating diseases by anabolic effect of enhancing growth hormone.

Group V, claims 17-18, drawn to method of treating osteoporosis by combination of compounds and bisphosphonates.

Group VI, claim 20, drawn to second process of making compounds (condensing carboxylic acids with piperidine).

The inventions listed as Groups I-VI do not relate to a single inventive concept under PCT Rule 13.1 because application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the combinations of categories:

(1) A product and a process specially adapted for the manufacture of said product; or
(2) A product and process of use said product; or
(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or
(4) A process and an apparatus or means specifically designed for carrying out the said process; or
(5) A product, a process specially adapted for the manufacture of the said product and an apparatus or means specifically designed for carrying out the said process.

Groups II-V are independent categories of inventions encompassing from increasing growth hormone by combination GH secretagues, increasing feed efficiency, treating anabolic diseases to treating osteoporosis. Group VI is an additional process of making compounds. Therefore, unity of invention was not found per combinations of categories under PCT Rule 13.1. See 37 CFR 1.475(d).